THE CAROTID-SINUS SYNDROME

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THE carotid-sinus syndrome may be defined as the occurrence of spontaneous symptoms precipitated by a hypersensitive carotid-sinus reflex. Appropriate stimulation of the left or right carotid sinus will induce detectable circulatory changes in many subjects (Robinson 1939, Galdston 1943, Nathanson 1946). The extent of such changes varies widely with the subject and with the technique of stimulation, and it is essential to differentiate the clinical syndrome from simple hyperreactivity of the carotid-sinus reflex which may be present without causing symptoms. It is not uncommon to meet a middle-aged or elderly patient in whom relatively light stimulation over one or other carotid sinus will produce instant cardiac standstill. These patients frequently deny, however, any history of symptoms which could be attributed to spontaneous activation of the reflex. The diagnosis of the carotid-sinus syndrome is permissible only if external stimulation of the affected sinus exactly reproduces, in whole or in part, the spontaneous symptoms of which the patient complains.

The circulatory effects of carotid-sinus stimulation were first described by Parry in 1799. He wrote: "in patients whose hearts have been beating with undue force, I have often, in a few seconds, retarded their motions many pulsations in a minute by strong pressure on one of the carotid arteries". Nearly a century later Czermack (1866) demonstrated that the cardiac slowing observed by Parry was mediated through the vagus and the manœuvre became known as the "vagus pressure test". Hering (1927) established that the carotid sinus is richly endowed with sensory nerve-fibres and forms the receptor organ of the reflex responsible for the effects originally observed by Parry. It is now, of course, well known that the carotid sinus forms an integral part of the baroceptor system regulating the peripheral vascular resistance and the heart-rate. Modern work on the anatomy and the neural connections of the carotid sinus, together with its comparative morphology, have been reviewed by Adams (1958).

Following isolated clinical observations (Roskam 1930), Weiss and Baker (1933) were the first to define clearly the clinical syndrome in man resulting from a hypersensitive carotid-sinus reflex. Contributions in the English literature, however, have been few (Turner and Learmonth 1948, Learmonth and Turner 1953, Behrman and Knight 1956).

We believe that a hypersensitive carotid-sinus reflex is a not uncommon cause of distressing and disabling symptoms in the middle-aged and elderly. The purpose of this paper is to describe sixteen patients in whom we have made this diagnosis in the past 2 years and in particular to emphasise the wide variety of clinical manifestations of the syndrome to which scant attention is paid in standard textbooks.

Methods

The technique for eliciting the reflex requires special mention. Since in patients with a hypersensitive reflex the fall of blood-pressure may be considerable, the patient should be recumbent. With the neck relaxed and the head turned slightly to the opposite side, the sinus can usually be located by feeling for the arterial pulse at the level of the superior border of the thyroid cartilage. We prefer to elicit the reflex by simple massage of the sinus, first on one side and then on the other, taking great care to avoid obstructing the carotid blood-flow. Simultaneous auscultation of the heart is essential, and as soon as cardiac standstill, abrupt slowing, or sudden pallor occurs, stimulation of the sinus is stopped. It is potentially dangerous to continue it after circulatory changes are evident, and for this reason we have not attempted to reproduce completely the more severe attacks which some patients described. When the patient has spontaneously confirmed that the premonitory symptoms of his more florid attacks (e.g., those with generalised convulsions or mental disorentiation) have been exactly reproduced, we have been content to accept the diagnosis. With these precautions, the procedure is perfectly safe.

Cardiac standstill or slowing is usually associated with pallor followed by flushing of the face. In many of the cases the intensity of the heart-sounds diminishes after standstill.

In thirteen of the cases we recorded the intra-arterial pressure directly during induction of attacks.

Clinical Findings

All sixteen patients in the series were male. Their ages at the time of diagnosis ranged from 48 to 82, and most of them had some hypertension. The right sinus was affected in fourteen and the left in two.

In conventional descriptions of the syndrome, the main clinical manifestations are generally given as sudden syncopal attacks, occasionally with convulsions and vertigo. Only five of our patients had such attacks, we therefore prefer the term "carotid-sinus syndrome" to "carotid-sinus syncope". The main presenting complaints were:

1. *Vertigo* (With involuntary movements in 2 cases and compulsive laughter in 1.)	6 patients
2. *Syncopal attacks* (With convulsions in 2 cases.)	5 patients
3. "*Focal*" *attacks*	3 patients
4. *Mental changes*	2 patients
Total	16

This grouping of the patients according to the main presenting features of their attacks shows the diversity of the clinical manifestation but does not imply any differentiation into specific clinical types. Although in each patient the pattern of attack tended to be stereotyped, there was a considerable overlap. Indeed, eight of the sixteen experienced vertigo at one time or another. In seven, head movement seemed to initiate some of the attacks, though this fact was usually elicited only by direct inquiry. Tying his tie was noted by one patient to induce an attack and physical exertion was blamed by two others.

A striking feature of many of the case-histories was the dramatic and abrupt first onset of symptoms, the initial episode being often the most severe and the longest. Five of the patients improved spontaneously during the first few months, attacks becoming less frequent and less severe.

VERTIGO

True vertigo was the symptom most often encountered. It was unassociated with nausea or vomiting or with tinnitus or perceptive deafness. All six patients in whom it was the presenting syndrome had noted that attacks were usually brought on by turning the head to one side (usually the right) or by flexing or extending the neck. In two of them a diagnosis of Ménière's syndrome had previously been made.

In the two cases summarised below, the attacks of vertigo were at some time associated with sudden involuntary movements of the trunk, and in one patient the first episode was ushered in with compulsive laughter.

Case 1.—Aged 70. First symptoms at 60. The onset was dramatic, for he recalled that, when standing in the street, he was seized with an urgent desire to laugh, and he immediately staggered backwards and fell heavily to the ground. He did not lose consciousness and recovered in a matter of minutes. Next day he noted that if he turned his head suddenly, to right or left, he would be seized with an intense vertigo and fall heavily to the ground.

He continued to have attacks of dizziness, and a diagnosis of Ménière's syndrome was made—for which he was treated for the next 7 years without improvement. Throughout this time he had noted that he could not wear any form of tight-fitting collar around his neck, since this increased the dizziness induced by sudden movements of the head. Another striking symptom was that if, when sitting in a chair, he extended his neck to look upwards, vertigo developed, and if he persisted in extending the head his body would arch and his legs would thrust forward. Once this happened when he was seated at a piano with his back to the wall and he thrust his feet through the lower panels of the instrument.

Apart from a blood-pressure of 180/100 mm. Hg, routine clinical examination was negative. Stimulation of the right carotid sinus produced immediate cardiac standstill followed by a typical attack of the vertigo he had experienced over the years. At first he was treated with belladonna but the response was poor. In December, 1957, denervation of the right carotid sinus was carried out and he has since remained free of all symptoms.

Case 2.—Aged 70. In August, 1958, he was sitting on a bed, tying his shoe-laces, when he suddenly developed flexion and extension movements of the trunk and hip. These involuntary movements went on for several seconds, to be followed by intense vertigo. Attacks of vertigo continued throughout the next day and he noted that if he looked upwards or downwards his discomfort was increased. He also noted occasional abrupt flushing of the face.

When he attended hospital in September, 1958, pressure on the right carotid sinus induced immediate cardiac standstill, pallor, and vertigo of the type he had noted previously. The cardiac standstill and vertigo were immediately followed by flushing.

After 2 months the symptoms lessened. Though residual symptoms now cause little disability, cardiac standstill and vertigo can still be induced by stimulating the right carotid sinus. A direct arterial-pressure trace showed a blood-pressure of 160/90 before such stimulation. After stimulation, asystole lasting 5·86 sec. occurred, and the arterial pressure fell to 40 mm. Hg; 5 seconds later the heart-rate had returned to normal but the blood-pressure was only 95/60; 70 seconds after stimulation the blood-pressure was still only 130/70.

SYNCOPAL ATTACKS

Syncope occurred in five patients. The attacks usually begin with transient faintness followed by loss of consciousness. Sudden pallor at the onset followed by flushing during recovery were often described by onlookers. Two patients volunteered the information that with minor attacks of faintness they themselves noted flushing of the face. Two had convulsive movements during an attack. One of these was incontinent of urine and was diagnosed as epileptic.

Case 3.—Now aged 53, he attended hospital at 45 with attacks he had had for eight years. They occurred once or twice a month and were sudden in onset, usually beginning with right facial discomfort. This was often followed by loss of consciousness during which his wife noted facial pallor followed by flushing. In the longer attacks conclusive movements of the limbs developed and he twice had incontinence of urine. In 1954, at the age of 47, he was fully investigated elsewhere. After air encephalography and electroencephalography had given negative results, a diagnosis of idiopathic epilepsy was made.

When seen in 1958, he admitted that an attack could be induced by turning his head sharply to the right. Pressure on the right carotid sinus reduced the blood-pressure from 160/100 to 100/50 with cardiac slowing, and a typical syncopal attack followed.

In view of his disability, surgical denervation was carried out on June 11, 1959. At operation it was found necessary to ligate a low superior thyroid artery. He had hemiparesis of sudden onset 48 hours after operation, but this disappeared in the next 14 days. He has had no further syncopal attacks.

"FOCAL" ATTACKS

Attacks of motor or sensory disturbances in the limbs were the main feature in three patients. In each case carotid-sinus stimulation produced cardiac standstill or slowing, with hypotension, and this was followed immediately by a typical attack. Two patients complained of unilateral sensory disturbance in an arm and leg. The third developed clonic movements of the right upper limb:

Case 4.—Now aged 48. At 40, he had suddenly lost consciousness while driving his car, which then mounted the pavement and crashed into a wall. After several months he recovered from his extensive injuries, but on returning to work he had attacks of dizziness which continued for the next 8 years. They were most frequent after he had been driving for any length of time. They generally then occurred when standing, and particularly if he suddenly looked upwards or downwards. If he did not quickly sit down, jerking movements of the right hand and arm would develop and persist for some seconds, and he would have to support himself to avoid falling.

In March, 1959, two months before we saw him, he was given a light general anæsthetic for dental extraction. While recovering from the anæsthetic he suddenly became cyanosed and deeply unconscious, and there was difficulty in feeling his pulse. Unconsciousness persisted for several hours, but he recovered without any permanent neurological sequelæ.

On clinical examination no abnormality was found apart from obesity. His blood-pressure was 160/95. Stimulation of the right carotid sinus induced pallor with abrupt slowing of the heart, followed immediately by clonic movements of both the head and the right arm with impairment of consciousness. These changes could be induced only when the patient was sitting. A direct arterial pressure record (with the patient recumbent) showed during right carotid-sinus stimulation an abrupt slowing of the heart-rate to 37 per min. with a fall of arterial pressure to 90/50. His disability was so great that denervation of the sinus was advised. He is now free from attacks.

MENTAL CHANGES

Mental changes were the most prominent feature in two patients. In one of these recurrent syncopal attacks were followed by mental confusion lasting several hours. The other became permanently demented after prolonged cardiac standstill, illustrating the danger of these attacks:

Case 5.—Aged 73. First developed symptoms at 66, when he attended hospital complaining of attacks of unconsciousness.

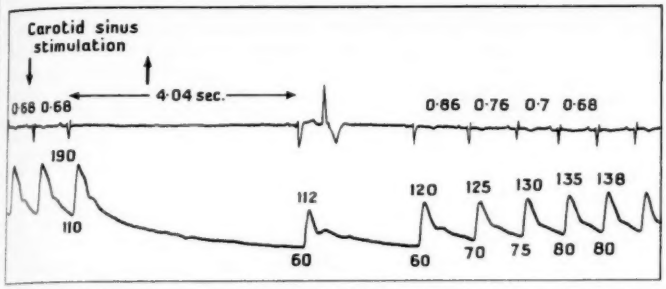

Fig. 1—Arterial pressure trace recorded at 25 mm. per sec. paper speed of induced attack with standstill lasting 4·04 sec.

Cycle length before standstill 0·68 sec. Blood-pressure 190/110. The 5th cycle after standstill has returned to 0·68 sec. but the blood-pressure is only 135/80.

These were sudden but usually brief, and his relatives noticed that they were almost always associated with pallor and were precipitated by sudden turning of the head to the right. At that time the only abnormality found on clinical examination was that the lightest touch on the right carotid sinus would induce immediate cardiac standstill and syncope, indistinguishable from his attacks.

The attacks continued during the next 2 years, and in 1954, while in church, he suddenly lost consciousness. He did not recover as rapidly as in the past and he was thought to be dead. He finally regained consciousness after 30 minutes, the actual time of cardiac standstill being unknown. When he was admitted to hospital immediately after this, dementia with signs of bilateral pyramidal involvement in the lower limbs were noted.

Since this episode the dementia has lessened slightly; but he has never returned to his normal mental state, and evidence of bilateral pyramidal involvement still persists. The attacks of unconsciousness still continue though never as severe as the episode in 1954. The lightest stimulation of the right carotid sinus still produces immediate cardiac standstill, whose duration varies with the vigour of stimulation. His disability is now primarily due to irreversible mental change, and, although medical treatment has not controlled his attacks, operative treatment has not been advised.

Circulatory Changes in Attacks

The arterial pressure changes during induced attacks were recorded in thirteen cases. With the patient recumbent, an indwelling needle was introduced into the right brachial artery and lead III of the electrocardiogram was used as a reference trace. In every case, carotid-sinus stimulation induced both disturbance of the heart rhythm (abrupt slowing or standstill) and a sharp fall in the mean arterial pressure and pulse pressure. The electrocardiographic changes induced by carotid-sinus stimulation are too well known to merit detailed description. The cases, however, fall conveniently into three groups, according to the mechanism of cardiac slowing:

1. *Standstill.*—If this is defined as ventricular asystole lasting 3 sec. or more, it occurred in five cases. The duration of standstill was 4–5 sec. in four and 9·6 sec. in the fifth. The heart-rate then returned to normal within a few cycles. With one exception there was simultaneous auricular standstill during the period of ventricular asystole. (Standstill also occurred in two other patients in the series in whom direct arterial pressures were not recorded.)

2. *Sinus bradycardia.*—In five cases, abrupt slowing was due to simple sinus bradycardia with occasional nodal escape beats.

3. *Auricular standstill.*—In the remaining three cases there was abrupt auricular standstill with an idioventricular escape rhythm with rates of 33–37 per min.

In the last two groups the period of slowing was fairly constantly about 6–10 sec. and was always followed by a phase of simple sinus tachycardia.

The broad pattern of behaviour of the blood-pressure was closely similar in the three groups. In the patients with standstill, the pressure fell exponentially during asystole. At the end of asystole it was 35–50 mm. Hg in the five cases. (In the erect position the effective intracranial arterial pressure would of course have been substantially lower.) After standstill, the diastolic pressure and pulse pressure were greatly reduced, climbing slowly in successive beats to reach their original level in 15–70 sec. (fig. 1).

An example of standstill recorded with a paper speed of 2·5 mm. per sec. is shown in fig. 2 (*a*). The delay in recovery of the pressure is well seen. The undulations of the pressure during this phase were a characteristic but not invariable finding.

An induced attack in the same patient 2 minutes after intravenous injection of atropine sulphate 1 mg. is shown in fig. 2 (*b*). Asystole is replaced by sinus bradycardia (this was confirmed at normal paper speed). During the period of slowing both systolic and diastolic pressure show an exponential fall, and the undulating pattern during recovery is closely similar to that following standstill.

In the eight patients with abrupt slowing the blood-pressure behaved almost exactly as in fig. 2 (*b*). In five the lowest systolic pressure reached was 100 mm. Hg with a diastolic of 30–60. In the other two, the pressure fell to 75/60 and 70/40. During the recovery phase, it climbed slowly, often in undulant fashion, as in the patients with asystole.

In all thirteen cases, the hypotensive effect of carotid-

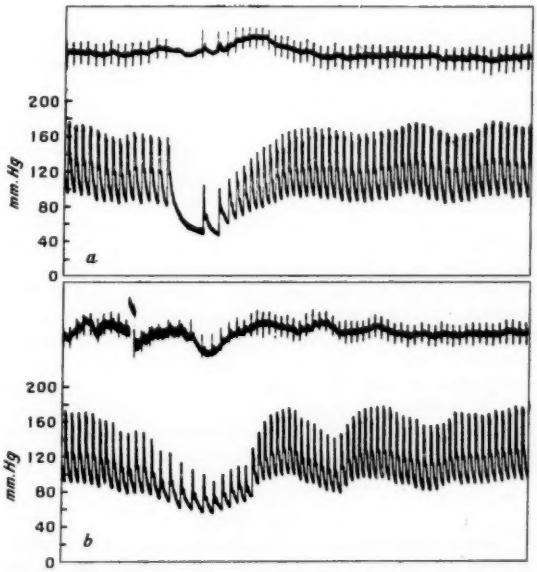

Fig. 2—(*a*) Arterial pressure trace recorded at 2·5 mm. per sec. paper speed. Induced attack with standstill lasting 4·4 sec. (*b*) Arterial trace from same patient after atropine (mg.) intravenously. Note undulations of pressure during recovery.

sinus stimulation always outlasted the effect on the heart-rate, whatever the mechanism of slowing. The sharp reduction in the mean arterial pressure and pulse pressure during slowing or after asystole must therefore be due either to an associated fall in peripheral vascular resistance or to a reduced cardiac output.

External stimulation of the sinus through the skin and subcutaneous tissues of the neck is clearly a crude method of eliciting the reflex. We would therefore feel considerable reserve in relating the circulatory changes we have found during induced attacks to those occurring in spontaneous clinical episodes. It is likely that in clinical attacks the reflex is usually initiated by pressure changes within the sinus, and the circulatory changes resulting may not be the same.

In the so-called cerebral form of the syndrome, symptoms can, it is said, be induced by carotid-sinus stimulation without demonstrable circulatory change. In all our cases, however, the induction of symptoms was always associated with circulatory changes. Nevertheless, we have been impressed by the occasional lack of correlation between the extent of the circulatory changes and the severity of the symptoms induced. In particular, in one patient stimulation of the right carotid sinus was followed by abrupt slowing of the heart, with a fall in pressure from 160/80 to 100/50 and a typical attack of vertigo. Stimulation of his left carotid sinus, however, produced standstill lasting 7·4 sec. during which his pressure fell to 15 mm. Hg but he denied that the resulting transient dizziness in any way resembled his attacks. Similar observations have been made by Galdston et al. (1943).

Treatment

Medical treatment consists in giving anticholinergic or sympathomimetic drugs so as to block the circulatory effects of the reflex. We have found belladonna the most useful drug, and in five of our milder cases the patient has reported considerable reduction in both the frequency and severity of the attacks whilst taking 15 minims of the tincture three times a day. The appropriate dose varies from patient to patient, but it should cause perceptible dryness of the mouth. In a few cases we have given ephedrine and isoprenaline without obvious benefit. It is usual to recommend that these patients avoid tight neckwear; but as many of our patients could induce symptoms by turning their heads to one side when they were stripped to the waist, the effects of a tight collar may have been exaggerated.

In the severe case the most satisfactory form of treatment is surgical denervation of the affected sinus, and this was advised in eight of our sixteen patients. If the onset is sudden and the history short, operation should be deferred, even though the symptoms are severe, because spontaneous remission may certainly occur. But persistence of disabling attacks for several weeks means that denervation should be advised. The risk of irreversible damage during a prolonged syncopal attack (case 5) has to be remembered. Other factors, such as symptoms when driving a car, must also be taken into account.

SURGICAL NOTE

(G. Gordon Crowe)

The operation consists in stripping the adventitia from the common internal and external carotid arteries for 3 cm. below and 3 cm. above the carotid bifurcation. With the patient's head rotated to the side opposite to the operative site, an incision was made along the internal border of the sterno-mastoid muscle. After ligation of the tributaries of the internal jugular vein, the arteries are freed from their bed in the carotid sheath. The adventitia is raised from the media of the common carotid and its branches by injecting beneath it through a fine needle a solution of 0·5% procaine. By sharp dissection with a scalpel the adventitia is then removed from the common carotid artery for the required distance and removal is continued distally for at least 2 cm. on the internal and external carotid arteries.

Difficulty due to the low origin of the ascending pharyngeal artery as described by Learmonth and Turner (1953) has not been encountered in this series. In case 3 trouble arose from a low superior thyroid artery, and the patient developed a hemiparesis 48 hours after operation. This complication would be a point against the suggestion of Learmonth and Turner (1953) that if difficulty is encountered in the region of the bifurcation it is best to clamp and divide the external carotid artery at its origin, close its origin with a running stitch of arterial silk, and ligate the distal end of the segment.

The wound is closed with subcutaneous sutures and clips and no special postoperative care is necessary. The patient is allowed out of bed on the day of operation or the next day.

Discussion

The symptoms of the carotid-sinus syndrome are generally attributed to cerebral ischæmia. In their classical paper Weiss and Baker (1933) divided their cases into three types according to the circulatory changes they considered responsible for the attacks. Their first or vagal type was attributed to cardio-inhibition with resulting abrupt slowing or standstill: these attacks could be prevented or abolished by atropine or adrenaline. The second or depressor type was attributed to peripheral vasodilatation and the attacks were prevented or abolished by adrenaline but showed no response to atropine. The third, or so-called cerebral, type showed neither cardiac slowing nor hypotension and was uninfluenced by atropine or adrenaline.

In our study of the intra-arterial pressure changes during induced attacks, we recorded in every case not only abrupt cardiac slowing or standstill but also a fall in pressure which could not be accounted for by the change in heart-rate alone. Admittedly our observations are limited to thirteen patients (each of whom presented with spontaneous attacks); but we do not yet see any real justification for a sharp division of cases into vagal and depressor types. Both factors appeared to be operating in every patient, though their relative importance differed. Syncopal attacks are due to transient generalised cerebral ischæmia resulting from a fall in the effective intracranial arterial pressure either from cardio-inhibition or from a fall in systemic pressure or (as we believe to be most common) from both.

Such a mechanism, however, does not explain why in some patients the ischæmia, judging by the neurological symptoms, is mainly in one or other cerebral hemisphere or the brain-stem. In these cases, we suggest, its location may be determined by concomitant cerebrovascular disease which is common in men of the age at which the syndrome appears. A case we have seen lately lends some support to this view:

The patient had a left hemiparesis due to cerebral thrombosis a year previously. The site of the vascular occlusion, whether intracerebral or extracerebral, was not known, since angiography was not considered justifiable. Stimulation of the right carotid-sinus reflex induced cardiac slowing and hypotension, and this was associated with paræsthesia of the left arm and leg with intensification of the weakness. After intravenous

atropine the circulatory changes no longer occurred and firm compression of the carotid sufficient to obliterate the pulse failed to induce an attack. It seems reasonable to assume that the reduced arterial pressure following carotid-sinus stimulation could no longer maintain an adequate blood-flow through collateral channels.

In patients with stenosis rather than occlusion of an intracerebral vessel any fall in the mean arterial pressure will lead to relative ischæmia in the territory supplied by the narrowed vessel (Denny-Brown 1951, Denny-Brown and Meyer 1957). In some cases of the syndrome the onset of symptoms is so sudden as to suggest that occlusive vascular disease is an integral part of their pathogenesis, the cerebral circulation being no longer able to tolerate fluctuations in the mean arterial blood-pressure.*

At present there is controversy over the so-called cerebral type of the syndrome. The main difficulty in accepting this entity is that the effector neural pathway has not been clearly demonstrated. Gurdjian et al. (1958) have denied that the cerebral type exists: the patients they believe are people with cerebral vascular disease who develop symptoms as a result of carotid-artery compression. Engel (1959), on the other hand, has criticised this explanation and has adduced clinical evidence in favour of the cerebral type. We ourselves have yet to see a case in which symptoms could be produced by carotid-sinus stimulation without simultaneous circulatory change. Galdston et al. (1943) demonstrated that in some patients stimulation of one carotid sinus would induce syncopal attacks with very slight pressure changes whereas stimulation of the contralateral sinus induced a greater fall in pressure but no syncope. A similar finding in one of our cases has already been mentioned. We feel that, on the evidence available, the possibility of a cerebral component of the carotid-sinus reflex cannot be dismissed.

Probably many cases of the syndrome are overlooked through lack of awareness of the condition. The clinical diagnosis should not present difficulty if one bears in mind the protean nature of the symptoms which hypotension may produce in people with cerebral vascular disease, overt or latent. When a middle-aged or elderly patient presents with symptoms which are consistent with attacks of cerebral ischæmia, local or general, the diagnosis of carotid-sinus syndrome should be considered. It can readily be confirmed at the bedside by reproducing a typical attack on carotid-sinus stimulation.

Summary

Sixteen cases of carotid-sinus syndrome seen within two years are reviewed.

The main presenting symptoms were vertigo, syncope, focal attacks, and mental changes. One patient was under treatment for idiopathic epilepsy, while another developed permanent dementia through cerebral ischæmia during temporary cardiac standstill.

In cases which do not respond to atropine or other drugs, attacks may be abolished by denervation of the affected sinus.

Arterial pressure changes recorded during induced attacks are described, and the pathogenesis of the syndrome is discussed.

* Electroencephalographic studies in cases with focal attacks would have been of interest, but unfortunately at the time this work was done the necessary facilities were not available to us.

References at foot of next column

DIAGNOSIS OF BRAIN ABSCESS IN INFANTS AND CHILDREN

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CASE-REPORTS of brain abscess in infants and children are comparatively rare, and with the marked decrease in the incidence and severity of infections, mainly through the use of antibiotics, the number has further diminished. The case-mortality, however, remains high and the main reason seems to be difficulty in diagnosis.

The purpose of this paper is to report 35 cases treated in Birmingham in the past ten years, to review the salient clinical features, and to discuss the diagnosis in the hope that this may help in earlier recognition.

The rarity of cerebral abscess in the first month of life is indicated by the fact that Butler et al. (1957) could find only 4 recorded cases to which they added 2 of their own. Of these 6 infants, only 1 (Farley 1949) survived. Baumoel et al. (1942) found 26 reported cases of abscess in infants under 1 year of age and added 1 of his own. Included in his series were 20 reported by Sanford (1928). Further cases have been described by Munslow (1957) and others. Very few indeed of all these have survived.

After infancy the incidence of brain abscess is considerably higher. One of the first large series to be reported was that of Holt who in 1898 reviewed 32 cases of cerebral abscess in children. Since then there have been many reports, in most of which the condition has been associated with chronic middle-ear infection or sinusitis, congenital heart-disease, chronic lung disease, or occasionally trauma. Although middle-ear infection seems to be by far the commonest predisposing factor in children, clinicians have long been aware that children with congenital heart-disease—particularly Fallot's tetrad—are prone to this complication. Gluck et al. (1952) collected 44 such cases, of which 23 were in children between 3 and 13 years of age: only 4 were successfully operated upon. Of the classical series of 1000 cases of congenital heart-disease examined post mortem by Abbott (1936), 7 had cerebral abscess; but in some cases the brain was not examined. Other authors, such as Maronde (1950) and Hanna (1941), have put the incidence higher than this. Newton (1956), in a modern account of the problem, refers to 72 cases and adds 7 of his own.

DR. HUTCHINSON & DR. STOCK: REFERENCES

Adams, W. E. (1958) Comparative Morphology of the Carotid Body and the Carotid Sinus. Springfield, Ill.
Behrman, S., Knight, G. (1956) *Brit med. J.* ii, 1523.
Czermack, J. (1866) *Z. Med. Naturw.* **2**, 384.
Denny-Brown, D. (1951) *M. Clin. N. Amer.* **35**, 1457.
— Meyer, J. S. (1957) *Neurology*, **7**, 567.
Engel, G. L. (1959) *ibid.* **9**, 565.
Galdston, M., Goldstein, R., Steele, J. M. (1943) *Amer. Heart J.* **26**, 213.
Gurdjian, E. S., Webster, J. E., Hardy, W. C., Linder, D. W. (1958) *Neurology*, **8**, 818.
Hering, H. E. (1927) Die Karotissinusreflexe auf Herz und Gefässe. Dresden.
Learmonth, J. R., Turner, R. (1953) British Surgical Practice. London.
Nathanson, M. H. (1946) *Arch. intern. Med.* **77**, 491.
Parry, C. H. (1799) An Inquiry into the Symptoms and Causes of the Syncope Anginosa. Bath.
Robinson, L. J. (1939) *Arch. Neurol. Psychiat.* **41**, 290.
Roskam, J. (1930) *Pr. méd.* **39**, 590.
Turner, R., Learmonth, J. R. (1948) *Lancet*, ii, 644.
Weiss, S., Baker, J. P. (1933) *Medicine, Baltimore*, **12**, 297.

The Series

The ages of our 35 children ranged from 5 weeks to 14 years (average 7½ years). In 2 of the 5 cases in infants, the cerebral abscess was secondary to neonatal sepsis. Males were in the majority—29 of the 35.

In all but 5 the primary source of infection, or predisposing factor, was reasonably certain. 18 had evidence of infection of the middle ear, 3 of nasal sinuses. Both neonatal cases had at the outset a cellulitis of the left side of the face involving the nose, and 1 of them went on to develop an osteomyelitis of the left maxilla (case 5, below). In 1 case the primary source of infection was skin sepsis—following transfusion into a scalp vein—which progressed to involve the underlying parietal bone. In 3 cases there was a definite history of trauma, while a further 4 were associated with congenital cardiac abnormalities. In 3 no primary source of infection was ever manifest. (In Sanford's review of 18 cases in children he was able to discover a suppurating focus in 12, of whom 5 had otitis media.)

The situation of the abscess was cerebellar in 9, frontal in 9, temporal in 10, and parietal in 10; 1 was in the brain-stem and 1 was multiple in both hemispheres. Judging also from other reports, the site of an abscess is three to four times more often the cerebrum than the cerebellum. As to outcome, 3 of the 9 children with cerebellar abscess died, but 18 of the 25 with supratentorial abscess were successfully operated upon. 2 of the 4 infants died, one of the survivors being diagnosed at 6 weeks following sepsis at 2 weeks of age.

In only 4 cases was an organism cultured directly from the cerebrospinal fluid (C.S.F.) though in another 5 cases organisms were seen on direct smear. The predominating organisms in the abscesses were staphylococci, pneumococci, and streptococci. (*Staph. aureus* has been predominant in the majority of reported cases.) Mixed organisms, particularly of intestinal type, are less common in children than in adults. The findings of 12 cases in the Children's Hospital and 23 cases admitted directly to one or other neurosurgical unit in Birmingham are summarised in the table.

ANALYSIS OF CASES

—	Neurosurgical units	Children's Hospital
Number	23 cases	12 cases
Age	4 mos. to 13 years (average 8½ years) 1 infant	5 weeks to 14 years (average 5 years) 4 infants
Interval	2 weeks to 3 mos. (average 5½ weeks)	1 week to 3 mos. (average 5 weeks)
Primary	12 ear; 3 sinus; 2 trauma; 2 heart; 1 skin; 3 uncertain	6 ear; 3 superficial; 1 ? chest; 2 unknown
Site	8 temporal; 6 frontal; 3 other supretentorial; 5 cerebellar; 1 brain-stem	2 temporal; 3 frontal; 3 parietal; 4 cerebellar
Result	17 recoveries; 6 deaths	7 recoveries; 5 deaths
Headache	Present, 22; not known, 1	Present, 8; 4 infants
Vomiting	Present, 15; absent, 7	Present, 10; absent, 2
Meningism	Present, 17; absent, 5	Present, 7; not noted, 5
Convulsions	Present, 3; absent, 19	Present, 6 (3 infants); absent, 6
Mental state	Impaired, 19; not noted or normal, 4	Altered, 11; not noted, 1 (infant)
Leucocytosis	Above 10,000 cells, 7; below, 6; unknown, 9	Above 10,000 cells, 8
C.S.F. cells (per c.mm.)	Up to 6000 (average 850); not known, 4	Up to 500 (average 140)
Protein (mg. per 100 ml.)	10–500 (average 115); not known, 8	Normal to 360 (average 90)
Bradycardia	Present, 5; absent, 14; not known, 4	Present, 5; absent, 7
Pyrexia	Present, 8 (up to 103°F)	Present, 4 (up to 102°F)
Focal nervous signs	Present, 19; absent, 1; doubtful, 3	Present, 10; absent, 2
Papillœdema	Present, 13; later, 3; absent, 7	Present, 7; absent, 5
C.S.F. organisms	Present, 5	Staphylococci, 2
C.S.F. culture	Present, 2	Staphylococci, 2
Special investigations	Ventriculography, 10; angiography, 1; encephalography, 1	Ventriculography, 5
Treatment	Tapped 23; excised, 4	Tapped 9; excised, 2

Illustrative Cases

Case 1.—Aged 14 years. First seen in Children's Hospital on March 13, 1957. Severe headaches for six weeks; losing weight and irritable. Seven months previously had discharge from right ear; two years ago had otitis media on left side. April 16: thorough examination elsewhere revealed right suppurative otitis media, increase of C.S.F. pressure, and mastoiditis, but no other sign of intracranial complication. Admitted to Children's Hospital on April 18 with vomiting and headaches; white blood-cells 16,300 per c.mm. (79% polymorphs); fundi normal; pupils dilated. April 20: flaccid weakness in all limbs; pulse-rate 90. C.S.F.: pressure normal; protein 70 mg. per 100 ml.; cells 36 per c.mm., mainly polymorphs. Later that day the pulse-rate suddenly slowed to 40. She became completely unconscious and she died soon after.

Necropsy revealed a cerebellar abscess from otitis media and mastoiditis.

Case 2.—Aged 3 years 4 months. Admitted to Children's Hospital in September, 1951. Seven weeks previously had suddenly lost the use of his right forearm and hand for twenty-four hours. Two weeks later had developed severe paroxysmal headache and vomiting, and two weeks after that had had a focal convulsion on the right side. There had been headaches, vomiting, and loss of weight with progressive weakness of right limbs. Examination showed right hemiplegia, bilateral papillœdema, and slight pyrexia. The conscious level deteriorated and hemiplegia became more pronounced. Three weeks after admission he had a further jacksonian convulsion, developed unequal pupils, and was transferred to a neurosurgical unit in a state of decerebrate rigidity. Sept. 27: burrholes and tapping of chronic left parietal abscess, which was eventually enucleated two weeks later. Good recovery except for residual right hemiparesis.

Three and a half years later again complained of headache and vomiting which persisted for four months. Ventriculogram showed a space-occupying lesion on the left side. At craniotomy an astrocytic glioma was removed from the left parietal lobe. The patient recovered but was left with right hemiplegia and hemianopia.

Case 3.—Aged 11 years. Previous history of colds and myringotomy four times. Six weeks before admission to the Children's Hospital on April 27, 1953, she began to have headaches and vomiting. At that time she had left otitis media with discharge, treated with penicillin; increasingly severe headaches, daily vomiting, and drowsiness. On admission: chronic otitis media (left), right facial weakness, fundi normal, pulse-rate 56, white blood-cells 10,000 (65% polymorphs). C.S.F.: 80 white cells per c.mm. (mainly lymphocytes); protein 60 mg. per 100 ml.; sugar 61 mg. per 100 ml. Thirteen days after admission she became comatose, her pulse-rate fell to 44, and she was taken urgently to the theatre where burrholes revealed a left temporal lobe abscess from which 50 ml. of pus was aspirated containing hæmolytic streptococci. After repeated tapping of the abscess she recovered, but she had right homonymous hemianopia and mild nystagmus.

Case 4.—Aged 5 years. Admitted to Children's Hospital on June 18, 1948. Head injury with momentary unconsciousness four months previously. Uncomplicated scarlet fever just afterwards, followed two weeks later by severe headache and vomiting. These symptoms persisted intermittently for three and a half months, becoming more severe towards the end of that period. He became listless and fretful, and had two convulsions which promoted admission. On examination: stupor; pulse-rate 70; pupils dilated; bilateral papillœdema, with a few hæmorrhages; nystagmus on looking to the right; and incoordination of right arm and leg. White blood-cells 24,300 (80% polymorphs).

Transferred to neurosurgical unit where burrholes revealed a right cerebellar abscess which was tapped. Uneventful recovery.

Case 5.—Aged 3 weeks. At 2 weeks had an inflammatory swelling round the left eye; despite penicillin this spread to the face and nose, and after a week there were early X-ray changes of the left maxilla involving also the left orbital bone. Various antibiotics were administered. Nine days later had a convulsion and C.S.F. showed a protein of 200 mg. per 100 ml. Some improvement followed, but six weeks after admission vomiting started with pyrexia and neck stiffness. The fontanelle bulged, lumbar-puncture pressure was 280 mm., and C.S.F. contained 480 white cells (44% polymorphs and 62% lymphocytes); the protein was 80 mg. per 100 ml., the sugar 56 mg. White blood-cells 14,300 per c.mm. Cannulation of the brain revealed a small quantity of pus in the left frontal lobe, from which *Staph. aureus* was grown. Ventriculogram at the same time gave evidence of a mass in the left parietal region; an infected subdural hæmatoma was aspirated.

Two weeks later pressure was still high and 60 ml. of purulent fluid was again aspirated from the subdural cyst. A week later the abscess was completely drained by burrholes after which the condition improved steadily and the child was discharged in three weeks. Residual right homonymous hemianopia.

Case 6.—Aged 5 weeks. Admitted to the Children's Hospital on March 3, 1956. At 2 weeks of age developed inflammatory swelling involving left side of nose and left eye. Discharge of pus from nose. Two weeks later became fretful, refused feeds, and started vomiting. The fontanelle was full, the temperature 100°F, and the pulse-rate 148; white blood-cells 19,300 (70% polymorphs). Next day he was worse; C.S.F. contained 500 white cells and protein was 360 mg. per 100 ml. That evening he had a convulsion; a ventricular tap was done through the fontanelle and 40 ml. of pus was obtained from the left frontal region from which *Staph. aureus* was grown. By the next day the child had a right facial weakness and right spastic hemiparesis. A ventriculogram confirmed a left intracerebral abscess which was aspirated on a number of occasions. The infant developed increasing hydrocephalus and was shown to have a block at the foramen of Monro, and also at the aqueduct of Sylvius. Despite attempts at shunting the fluid, the hydrocephalus increased in size and the child died at the age of a year.

Symptoms

Diagnosis of a brain abscess in a child is often very difficult, leading to a dangerous delay in treatment. The significant diagnostic features may be divided into four main groups. First, those due to raised intracranial pressure, such as headaches, vomiting, papillœdema, and bradycardia. Secondly, those of intracranial suppuration, such as irritability, drowsiness or stupor, meningitic signs, and loss of weight. Thirdly, general signs of infection, including fever, chills, and leucocytosis. Fourthly, signs of local involvement of the brain, such as focal convulsions, cranial-nerve palsies, field defect, aphasia, ataxia, or paresis.

A carefully obtained history of previous infection, especially of otitis media, together with the development of symptoms of raised intracranial pressure, is usually of major diagnostic importance, and then abnormal physical signs furnish localising information. The interval between the onset of infection and the diagnosis of a cerebral abscess is usually fairly long—over ten days as a rule. Only one of our cases had an interval as short as one week, and this proved really to be necrotic encephalitis rather than an abscess with cavitation.

Headache

Headache seems to be the most important and most constant early symptom. It was a prominent feature in every one of the 29 children in our series over 1 year of age. In most cases the headaches were severe, being usually paroxysmal but occasionally persistent. Sometimes they were confined to the side of the lesion, and in several of the cerebellar cases there was a history of occipital headaches. However the headaches are often more generalised and they may occur at various times of the day, commonly in the early morning or at night. Especially if preceded by infection such as otitis media, or by trauma, continued headaches in a child should never be accepted as of no consequence. Every effort must be made to exclude intracranial suppuration.

In our series the time between onset of headaches and diagnosis or death varied from two weeks to four months. In the 12 children who died, the average was five weeks. The difficulty therefore does not arise from rapid progress of the disease, but lies in interpretation of the symptoms.

Vomiting

With the headaches, there is often also a history of vomiting. Usually the child begins to vomit once or twice daily soon after the start of the headaches. There was a clear history of vomiting in about two-thirds of our cases, though in some of these it came on only in the later stages of the disease. The vomiting was not always projectile; indeed Letelier (1945) reported that this type of vomiting was seldom seen in his cases. Anorexia is often an associated symptom, and with or without vomiting it may lead to quite severe loss of weight in a relatively short time. The clinical picture may then resemble that of tuberculous meningitis or cerebral tumour.

Convulsions

A convulsion is a dramatic incident which usually precipitates investigation, and it may be of important localising value if it is focal. In our series, however, only a quarter of the children had convulsions. As might be expected, these were commoner in infants than in the older children: in 2 infants a focal convulsion was the first sign of intracranial involvement following infection elsewhere. Baumoel (1942) stated that nearly all the 26 infants reviewed by him had convulsions, either focal or general: in many these were the presenting symptom, but in others they were preceded by vomiting and restlessness. A focal convulsion in an infant with a history of infection should always bring to mind the possibility of a brain abscess. In older children convulsions started some weeks after the onset of headaches and vomiting: in 2 of these they were focal and were the first definite sign of serious intracranial disease.

Mental Disturbance

Some degree of mental disturbance is *always present* though the form may vary from case to case. The child commonly becomes irritable and fretful, is unable to concentrate, and is vague in answering questions. Shortly afterwards he may be seen to tire easily and he then becomes lethargic and apathetic and tends to sleep excessively. Gradually he becomes drowsy: and once he reaches this stage treatment is urgent, for he may suddenly lapse into coma, after which death is not long delayed.

Infants

In infants by far the commonest presenting symptoms are vomiting and convulsions. At this age vomiting may have many causes, while convulsions may be a response to fever of any cause. Brain abscess, however, should be suspected if, with a history of infection or trauma, the child shows other evidence of intracranial disease—especially a full anterior fontanelle, an abnormally enlarging head, or cranial-nerve palsies. With other

observers, we have noticed that general signs of infection, such as rises in temperature, pulse-rate, or white-cell count, are of much greater diagnostic assistance in infants than in older children. Once the abscess becomes encapsulated, the temperature subsides and may remain normal.

Physical Signs

An abscess behaves in many ways like a tumour, producing signs of raised intracranial pressure such as slowing of the pulse and changes in the fundus of the eye. These changes, however, occur mainly at a late stage of the disease. In only 23 of our 35 cases was papillœdema present at *any* stage of the illness, and 6 of these proved to be cerebellar abscesses. Though swelling of the disc is commoner with a cerebellar abscess than with a cerebral one, even a large cerebellar abscess may not cause papillœdema at any stage, and this was so in 3 of our 9 cases. Nevertheless venous engorgement or blurring of the disc margin should be repeatedly looked for when the possibility of a brain abscess arises, for it may be one of the few clues to the diagnosis.

Bradycardia, particularly associated with leucocytosis, may be a further valuable pointer. This combination of signs was seen in 5 of our cases, though in 1 the bradycardia was only terminal. When the pulse-rate suddenly drops, treatment becomes very urgent. Signs of meningeal involvement, such as Kernig's sign, or evidence of actual brain damage, were noted at some stage in most of the cases. In the majority, however, they were a late manifestation, coming on some weeks after the headaches and vomiting. Meningeal irritation preceded other signs in 4 of the 5 infants. Focal neurological signs—cranial-nerve palsy, pyramidal disturbance, or field defect—were definite in 25 cases. In 3 cases of cerebellar abscess no focal signs were found; but the defective cooperation of the small child makes their recognition particularly difficult.

In some cases physical signs are fairly gross, but in the majority such slight changes as visual field defects or facial weakness may be missed unless carefully looked for. When present, physical signs are of great help in showing that there is an intracranial lesion, but other evidence will be necessary to confirm the diagnosis of intracranial suppuration. If the possibility of abscess is borne in mind, and the case is fully and promptly investigated, early diagnosis and successful treatment are probable. In a small proportion of cases there will be no focal signs whatsoever, and the diagnosis will rest entirely on the history, symptoms, and special investigations.

Investigations

The total *white-cell count* exceeded 13,000 per c.mm. in 14 out of the 22 cases in which it was done, and the proportion of polymorphs was usually 70–80%. In 8 cases white-cell counts remained within normal limits.

Lumbar puncture can be very dangerous if there is an intracranial space-occupying lesion, and it should not be undertaken if there is swelling of the optic disc. In most of our cases the C.S.F. had already been examined elsewhere.

The findings are seldom pathognomonic, but in conjunction with others they will help. In only 3 of our 26 cases in which C.S.F. was examined was the fluid quite normal. In 3 others the only abnormality was a raised protein level. In the remaining 20 the cells ranged from 12 to 6000 per c.mm., but mostly numbered about 100. Usually lymphocytes predominated, but occasionally polymorphs. An interesting feature seen in a few of the cases, in which several samples of C.S.F. were obtained, was a gradual reduction in the number of cells, which in one case fell from 59 to within normal limits. This presumably is what happens as encapsulation becomes more complete. The protein level of the C.S.F. was above the upper limit of normal in nearly every case. In 1 it reached 500 mg. per 100 ml., but in 8 cases it was 70–80 mg. In 5 cases the protein level exceeded 200 mg. No diminution in sugar or chloride content was noted in any of the fluids examined, and this may be useful in distinguishing brain abscess from tuberculous meningitis. The fact that in cases of brain abscess organisms are seldom grown from the C.S.F. may also be of help. Distinction from encephalitis and intracranial tumour may not be possible by examination of the C.S.F. alone.

Radiography of chest, skull, and mastoids should be done routinely where intracranial abscess is suspected. It may furnish important presumptive evidence, especially in cases of cerebellar abscess.

Electroencephalography may be a valuable aid especially in the differentiation of brain abscess from encephalitis. It may also yield strong evidence as to the site of the abscess. The focal disturbance seen is that common to any rapidly expanding intracranial lesion, and consists essentially in high-voltage delta activity in the vicinity of the lesion.

Ventriculography may be necessary for diagnosis or localisation, or possibly as a test of cure. Some of the more deeply seated hemisphere and infratentorial abscesses may not be demonstrable without detailed air studies. These should be performed only immediately before operation.

If the abscess is in the frontal or temporal lobe *carotid angiography* will reveal evidence of an avascular lesion.

Sometimes the only way of distinguishing an abscess from a neoplasm or hæmatoma is direct *surgical puncture*, and this should always be done in any case of doubt.

Differential Diagnosis

Differentiation of brain abscess from other conditions such as encephalitis and intracranial tumour may be very difficult. In encephalitis—a condition common in childhood—the interval between the onset of pyrexial illness and the intracranial complication is usually a good deal shorter than in abscess. The preceding history may be of vital significance: cases of encephalitis have often had a previous virus infection such as mumps, whereas brain abscess is commonly preceded by a pyogenic infection. The signs, symptoms, and C.S.F. findings may be identical in the two conditions.

Cerebral tumour has usually a somewhat slower onset, and the history and signs of pyogenic infection will be absent. Nevertheless it may be indistinguishable from abscess, except by direct surgical puncture.

Tuberculous and pyogenic meningitis seldom give rise to any serious difficulty except in their very early stages. A positive tuberculin reaction, and a low C.S.F.-sugar are the most important diagnostic features. Acute meningitis always gives a picture of high sustained fever, rapid pulse, delirium, and neck rigidity, and the C.S.F. findings are usually grossly abnormal.

Lateral sinus thrombosis seldom resembles cerebral abscess closely enough to cause much difficulty. Unilateral thrombosis of the sigmoid sinus is incidental to mastoiditis, and there are seldom signs indicating raised intracranial pressure or local disturbance of brain function.

Intracranial hæmatoma or effusion may on occasion closely resemble abscess and may require special investigations for their differentiation.

Treatment

Neurosurgical treatment is standard through a clean field. The abscess when located is tapped through a burrhole, and a sample of pus is taken and tested for organisms together with their sensitivity. Penicillin and streptomycin are inserted, and as soon as the organism is known the initial treatment is replaced as necessary by specific antibiotic therapy. The progress of the abscess is followed by insertion of a water-soluble contrast medium on the first two occasions when it is aspirated, with subsequent X-rays of the skull to show outlines of the abscess cavity. Only if the abscess fails to sterilise or collapse is removal of the capsule undertaken later. If diagnosis is made in time, results are good.

Summary

Any child who still has symptoms or signs of cerebral dysfunction more than ten days after the onset of an infective illness, especially involving the ear, nasal sinuses, or respiratory tract, should be suspected of having a cerebral abscess until this is disproved. Of special importance in diagnosis are persistent headache, listlessness, and drowsiness, and in infants focal convulsions. Focal signs may be slight, in which case the diagnosis rests on the history, symptoms, and relevant special investigations.

35 cases are analysed with a view to promoting earlier diagnosis and consequently earlier and more successful treatment.

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REFERENCES

Abbott, M. E. (1936) Atlas of Congenital Heart Disease. New York.
Baumoel, S., Silber, T. B., Hyman, L. J. (1942) *Arch. Pediat.* **59**, 711.
Butler, N. R., Barrie, H., Paine, K. W. E. (1957) *Arch. Dis. Childh.* **32**, 461.
Farley, D. L. B. (1949) *Lancet*, i, 264.
Gluck, R., Hall, J. W., Stevenson, L. D. (1952) *Pædiatrics*, **9**, 192.
Hanna, R. (1941) *Amer. J. Dis. Child.* **62**, 555.
Holt, L. E. (1898) *Arch. Pediat.* **15**, 81.
Letelier, R. V. (1945) *Rev. Otorrinolar.* **5**, 236.
Maronde, R. F. (1950) *Ann. intern. Med.* **33**, 602.
Munslow, R. A., Stovall, V. S., Price, R. D., Kohler, C. M. (1957) *J. Pediat.* **51**, 74.
Newton, E. J. (1956) *Quart. J. Med.* **25**, 201.
Sanford, H. N. (1928) *Amer. J. Dis. Child.* **35**, 256.

A NEW SCREEN TEST AND SELECTIVE MEDIUM FOR THE RAPID DETECTION OF EPIDEMIC STRAINS OF STAPH. AUREUS

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THE investigation of hospital staphylococcal outbreaks has until now been greatly hindered by the lack of laboratory tests for rapidly identifying strains likely to give rise to epidemic infection in surgical and maternity units. That such strains of staphylococcus exist has been shown very clearly by phage-typing. Williams (1959), for instance, has pointed out that, although very many different phage-types have on occasion been isolated from septic lesions, only twenty or so have been isolated at all commonly, and, of these, only about six in his experience were often responsible for epidemics of hospital infection. Why these few types are potentially dangerous in hospitals is still unknown.

Although phage-typing has been indispensable in the epidemiological study of staphylococcal infections in hospitals, its value has been largely retrospective, as typing is done in relatively few laboratories and may be time-consuming. Thus, even under the most favourable circumstances, a delay of two or three days is likely between the collection of a specimen from patient or environment and the eventual report on the phage-type of the staphylococcus isolated from it, and for hospital laboratories without a local phage-typing reference centre the delay will be even longer.

Epidemic staphylococci are characteristically resistant to many of the commonly used antibiotics; and resistance to penicillin and tetracycline in particular may sometimes serve as a useful marker of epidemic strains, although a common pattern of antibiotic resistance is a poor guarantee of identity of phage-type in hospital strains. Other reactions given by certain strains of *Staphylococcus aureus*—e.g., the producton of opacity in egg-yolk media (Gillespie and Alder 1952) or in serum agar (Tomlinson and Parker 1956) may help in the rapid screening of particular strains of staphylococci in certain outbreaks.

A chance observation made during systematic studies of hospital staphylococcal infection in the Exeter clinical area, and especially at the Torbay Hospital, has led to the development of a test which apparently discriminates between epidemic and non-epidemic strains of *Staph. aureus*. The test depends on the greater resistance of the epidemic staphylococci to mercuric salts. By incorporating an appropriate concentration of mercuric chloride in peptone agar, this differential property of epidemic staphylococci has also been made the basis for a simple selective medium which has been successfully used for direct isolation of epidemic staphylococci from swabs and pus specimens, and from the hospital environment—e.g., from blankets and ward or theatre air.

Preliminary Observations

In the past few years intensive efforts have been made at this laboratory to devise new tests for the epidemic staphylococci—partly by laboratory examination of cultures collected locally or sent in for phage-typing from other laboratories, and partly by following up any lead, however tenuous, offered by careful observation of infected wounds. I am particularly indebted to Mr. A. M. N. Gardner, surgeon and control-of-infection officer to the Torbay Hospital, for his stimulating collaboration in this work.

In June, 1959, a number of type-80 staphylococcal wound infections occurred at the Torbay Hospital. Mr. Gardner discussed the possibility that the catgut in the wounds of the patients concerned might have been digested by the infecting staphylococci, as fragments of catgut extruded from the wounds seemed unduly soft. That certain staphylococci should produce a collagen-digesting enzyme seemed a possibility worth exploring, but no in-vitro evidence was found that the tensile strength of catgut was affected by immersion for several days in actively growing cultures of epidemic staphylococci. One of the batches of catgut examined during this study showed, however, an inhibitory effect against some staphylococcal strains but not against others, and further study of this differential inhibition led to the work described here.

The batch concerned was one of plain catgut, size 2/0 B.P., prepared under licence by Morley's process. In this method, the catgut is sterilised in aqueous iodine solution for eight days. It is then treated with an alcoholic solution of mercuric iodide, which helps to remove traces of iodine and also has a bacteriostatic effect. The catgut is finally packed into sterile tubes, which are filled with Seitz-filtered ethyl alcohol and immediately sealed.

In a rough orientating experiment, 3 in. lengths of this

catgut were cut off with aseptic precautions into four 10 ml. tubes of nutrient broth. The tubes were inoculated respectively with two type-80 strains, a phage-group III staphylococcus, and a coagulase-negative skin staphylococcus. After forty-eight hours' incubation, the two type-80 strains showed the degree of turbidity expected of a staphylococcal broth culture, while the group-III staphylococcus and the skin staphylococcus were still completely inhibited.

The experiment was repeated with other staphylococcal strains, using more adequate controls. Three type-80 strains, one of phage-type 52/52A/80, two other phage-group I strains, and single strains of phage-groups II and III were grown overnight in Lemco broth. Equal drops of the various cultures were then dropped from a Pasteur pipette into duplicate tubes of Lemco broth, one containing 3 in. of catgut and one serving as a control. The growth present after overnight incubation is shown in table I.

TABLE I—EFFECT OF CATGUT ON THE GROWTH OF STAPHYLOCOCCI IN BROTH

Strain no.	Phage-type of strain	Growth in broth with catgut	Growth in control broth
1	80	+++	+++
2	80	+++	+++
3	80	+++	+++
4	52/52A/80	+++	+++
5	29/52	−	+++
6	52	−	+++
7	3B/3C/55/71	−	+++
8	6/7/47/54	−	+++

The behaviour in catgut broth of the phage-group I strains tested was of particular interest. All three type-80 strains and the closely related type 52/52A/80 strain (Rountree 1959, Asheshov and Rippon 1959) were all resistant to the catgut effect, while the other two group-I strains were inhibited, as were the group-II and group-III strains. Agar plates containing suitable volumes of the fluid from the catgut tubes showed a very similar differential inhibitory effect on these staphylococci. Tests on agar plates with filterpaper strips impregnated with iodine or with mercuric salts indicated that the inhibitory effect was associated with the mercuric ion rather than with iodine. In later experiments, therefore, the catgut was dispensed with and mercuric salts were used in the development of the selective medium described below.

Quantitative Assessment of Differential Effect of Mercury on Staphylococcal Strains

Selective media have often been based on the differential activity of certain cations or anions against different bacterial groups. Potassium tellurite, sodium azide, lithium chloride, bismuth sulphite, and thallium acetate are examples of salts that have been used in this way. On the other hand, a cleavage through a single species such as *Staph. aureus* on the basis of resistance to mercuric ions raises certain problems. One might expect, for instance, that the minimal concentrations of mercury required to inhibit a series of staphylococcal strains would be distributed evenly about an average figure within a fairly narrow range. If this were the case, a consistent grading of any collection of staphylococci into strains resistant or sensitive to a particular concentration within this range would seem difficult to achieve.

As an essential preliminary to the study of the spectrum of staphylococcal resistance to mercury, the methods of testing this resistance were first standardised so as to ensure reproducible results. Early experiments showed that the differential effect of mercuric salts on the staphylococci picked out by the catgut test was no longer observed if the salt was added to the final medium before this was autoclaved. In later work, therefore, stock unheated solutions of mercuric salts were prepared and the appropriate amounts were added to broth or to melted agar just before use, to obtain the concentrations of mercuric ion required. Even with avoidance of autoclaving, however, mercuric potassium iodide—the salt used by the manufacturers in the catgut-sterilisation process—gave somewhat erratic results, possibly owing to the iodide radical (Carroll 1955). Reproducible results were obtained with mercuric chloride, and only this salt was used in later studies.

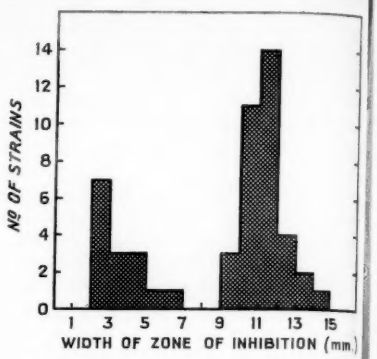

Fig. 1—Histogram of widths of zones of inhibition of 50 staphylococcal strains streaked on agar plates at right-angles to filter-paper strip containing 1 in 1000 phenylmercuric nitrate.

Screening tests were done with a number of epidemic and non-epidemic staphylococcal strains—so judged by their phage-types—in broth containing dilutions of mercuric chloride ranging up to 1 in 60,000. These tests showed that type-80 and some group-III staphylococci would grow in considerably higher concentrations of mercury than other strains of *Staph. aureus*, and that a suitable concentration of mercury could be chosen which would discriminate between two quite different levels of resistance to mercury salts. This was also shown by plate inhibition tests on a series of 50 unselected staphylococcal strains received for phage-typing. These strains were streaked on agar plates at right-angles to filterpaper strips impregnated with 1 in 1000 phenylmercuric nitrate—an organic mercurial disinfectant that gave wider zones of inhibition than mercuric chloride. The histogram of the widths of zones of inhibition obtained is shown in fig. 1.

The bimodal distribution shown in this figure again suggests a real difference between mercury-resistant and mercury-sensitive staphylococci. A distribution of this type was not obtained in tests with silver, copper, or cobalt salts.

In agreement with the well-known findings of other workers, the differential concentration of mercury that discriminated between mercury-resistant and mercury-sensitive staphylococci was also found to vary with the concentration of protein in the medium, particularly when blood or serum was incorporated in it. With the simple peptone-agar base described below, a concentration of 1 in 27,500 mercuric chloride was found to be a satisfactory discriminant level.

Preparation and Use of Mercuric Chloride Agar

The medium is made from a peptone agar base containing 'Oxoid' peptone 2%, sodium chloride 0·5%, and Davis agar 1%. The pH of the final medium is 7·4. It is bottled in 100 ml. amounts and autoclaved at 10 lb. pressure for fifteen minutes. As already mentioned, the mercuric chloride is added from a stock solution just before plates are poured.

Provided known resistant and sensitive staphylococcal control cultures are used, the mercuric chloride stock solution may be prepared from *B.P.C.* mercuric chloride tablets, solvellae hydrargyri perchloridi. One of these tablets dissolved in a pint of distilled water gives a 1 in 1000 stock solution which can be used for three to four weeks. This stock solution is not sterilised.

To prepare the medium, a bottle of peptone agar is melted and allowed to cool to 50°C. Then, 3·63 ml. of the agar is pipetted off and replaced by the same volume of 1 in 1000 mercuric chloride. The plates are poured immediately, dried at 37°C, and stored in the refrigerator. They are not used more than three days after preparation, as some mercury-sensitive strains begin to show growth on plates stored for four to five days.

The medium is inoculated with a large loopful from an overnight broth culture of the test strain; on a suitably ruled plate,

25-30 strains can be readily tested. After overnight incubation, one should see an all-or-none result—i.e., a circle of confluent growth or no growth. Occasionally, some strains may show a few discrete colonies on the mercury medium; these are re-tested. The results of a typical test on a mixed collection of strains subcultured to mercury agar and on to a control peptone agar are shown in fig. 2.

As occasional strains of skin staphylococci will grow on this medium, a slightly modified one on which *Staph. aureus* shows good pigmentation has been found very useful as a selective medium for direct plating of wound swabs or as a settle plate in air-hygiene studies in theatres or wards. The modified medium contains 5% of whole milk in addition to the ingredients mentioned above. The same concentration of mercuric chloride as in the original medium—1 in 27,500—has given satisfactory results. The addition of milk increases pigmentation; moreover, most staphylococcal strains also produce a pearly sheen due to lipase production in the medium around the colonies, particularly when Channel Island milk is used.

Both media, if used for direct plating of pus or swabs or as settle or sweep plates, have the further advantage that they

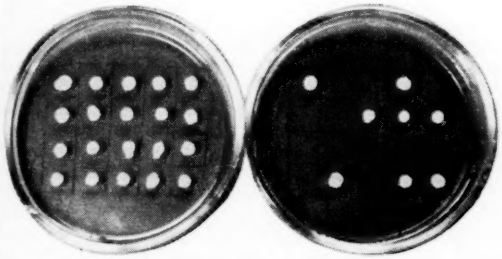

Fig. 2—Typical mercury-resistance test on 20 staphylococcal strains.
Control plate on the left shows confluent circles of growth of all 20 strains on peptone agar. Only 8 strains have grown on the right-hand plate, a peptone agar containing 1 in 27,500 mercuric chloride.

inhibit the swarming of most strains of proteus and the growth of many coliform organisms.

As an obvious corollary to the requirement that mercury-agar plates should not be stored for more than a few days, only *Staph. aureus* colonies that come up after overnight incubation can be classed as mercury-resistant. When plates are left on the bench for a few days after incubation, staphylococcal colonies may appear on them which in further tests from broth cultures on to freshly prepared medium show no growth.

Survey of Mercury Resistance of Staphylococcal Strains isolated from Hospital Material

An orientating survey of the mercury resistance of staphylococcal strains was done on a series of 505 cultures, isolated in our own laboratory or received for routine phage-typing from hospital or public-health laboratories in the South-West of England, from Bath and Bristol in the north to Truro in the south-west of the region. The strains were a highly selected series, inasmuch as they came from hospitals interested in the problems of staphylococcal infection, and were usually isolated in the course of investigations on hospital infection. The series included organisms isolated from the normal nose, throat, or skin; from wounds, skin lesions, various other parts of the body (e.g., from the genitourinary tract or fæces); and from blankets, air, or some other environmental source.

In all, 244 strains were mercury-resistant, 234 were mercury-sensitive, and 27 gave an equivocal result on first test, with one to twenty colonies on the mercury medium instead of a clear-cut result. Later work has shown that, on re-test, strains that have given an equivocal first result usually give confluent or no growth. Preliminary attempts to isolate mercury-resistant variants from strains showing no growth on mercuric chloride agar have so far failed.

TABLE II—RESULTS OF MERCURY-RESISTANCE TESTS ON STAPHYLOCOCCI OF PHAGE-GROUPS I, II, AND III, AND VARIOUS OTHER TYPES

Phage-group	No. of strains	Resistant	Sensitive
I	210	160 (*76·1%*)	50 (*23·9%*)
II	52	3 (*5·9%*)	49 (*94·1%*)
III	171	69 (*40·0%*)	102 (*60·0%*)
Type 187	3	1	2
Mixed types	12	..	12 (*100%*)
Untypable	30	11 (*36·6%*)	19 (*63·4%*)

TABLE III—DETAILED RESULTS OF MERCURY-RESISTANCE TESTS ON PHAGE-GROUP I STRAINS

Phage-type	No. of strains	Resistant	Sensitive
80	113	107	6
52/52A/80	31	30	1
29/80	7	6	1
52/80	8	7	1
79/80	1	..	1
29/52/80	2	1	1
52A/79/80	2	1	1
29/52/52A/80	3	2	1
52/52A/79/80	6	5	1
29/52/52A/79/80	1	1	1
29	7	..	7
52A	1	..	1
79	14	..	14
29/52	1	..	1
52A/79	8	..	8
29/52/52A	2	..	2
52/52A/79	2	..	2
29/52/52A/70	1	..	1

The relationships between mercury resistance and phage type, antibiotic sensitivity, and epidemic propensity of different phage-types were analysed from the findings of this survey, using only the data on strains that gave a clear-cut positive or negative result in the first mercury-resistance test done on them.

Relationship between Mercury Resistance and Phage-type

As phage-typing has until now been the only method that gave an indication of the capacities for epidemic spread of staphylococcal strains, the comparison of mercury resistance with phage-type was of particular interest.

The proportions of mercury-resistant and mercury-sensitive staphylococci in the three main phage groups and among various strains not belonging to these groups are shown in table II. It will be seen that 76·1% of group-I strains, only 5·9% of group-II strains, and 40·0% of group-III strains were mercury-resistant.

The results obtained in the mercury test on staphylococcal strains of phage-group I are shown in detail in table III. The strains are grouped into three subgroups in the table. The first subgroup comprises type-80 strains, together with strains typed as 52/52A/80, now recognised as closely related to type 80. Of the 144 strains in this category, 137 (95·1%) were mercury-resistant. 2 mercury-sensitive type-80 strains and the 1 mercury-sensitive type 52/52A/80 strain were isolated from wound swabs. The 4 remaining mercury-sensitive type-80 strains were isolated from eye (1), nose (1), urine (1), and ear (1).

The second subgroup of strains in table III includes all strains other than type 80 or 52/52A/80 that gave an 80 in the pattern obtained, either in the initial test with phages at R.T.D. (routine test dilution), or with 1000 R.T.D. if no reaction was obtained at R.T.D. On the clinical information available, some of these strains were undoubtedly highly pathogenic. Of this group, 23 (76·6%) were mercury-resistant. The third subgroup of group I contained 36 strains, all of which were mercury-sensitive. These included 8 strains falling into type 52A/79—a phage-type often associated with outbreaks of infection in infants in maternity nurseries but not as a rule with outbreaks of surgical infection.

The detailed results of mercury tests on phage-group-II strains are shown in table IV. Only 3 out of 52 strains were mercury-resistant. All 3 fell into phage-type 71—the type

shown by Parker et al. (1955) to be responsible for most cases of impetigo, and reported by Gillespie et al. (1957) as a cause of pemphigus neonatorum in infant nurseries. It is of particular interest, however, that of the 19 type-71 strains examined in this series, 15 isolated from superficial sites were all mercury-sensitive, while 3 out of 4 isolated from wounds were mercury-resistant.

The results of mercury-resistance tests on group-III strains are given in table V. This table is an abbreviated one, as 71 different phage patterns were reported on strains in this group, some of them so similar that by the ordinary conventions of reporting phage patterns (Williams and Rippon 1952) they would have been reported as identical. This table shows that certain types are predominantly mercury-resistant and others mercury-sensitive.

12 strains which gave a phage pattern spanning two or more phage groups were all mercury-sensitive. The recently described phage-type 187 was represented in this series by only 2 strains, 1 of which was mercury-resistant and the other mercury-sensitive. Finally, the series included 30 untypable strains, 11 of which were mercury-resistant and 19 mercury-sensitive.

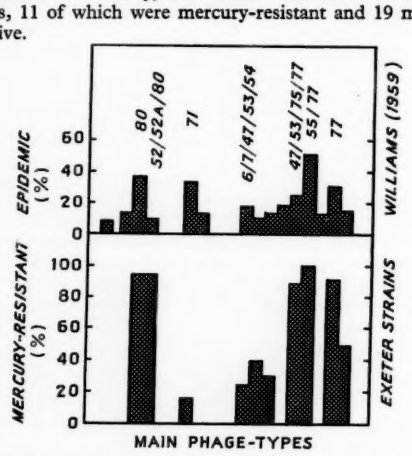

Fig. 3—Relationship between epidemicity and mercury resistance of certain important phage-types of staphylococci.

Upper part of diagram shows the percentages of strains of various phage-types that were epidemic in the study of staphylococcal strains from surgical units included in the paper of Williams (1959). Below are the corresponding percentages of mercury-resistant strains, in the same phage-types, in the present study.

The staphylococcal strains used as propagating strains for the different phages and serving as routine test strains for phage titration were examined by the mercury test. Types 80, 47, 53, 54, 75, 77, 83A, and 187 were mercury-resistant, and types 29, 52, 52A/79, 42D, 3A, 3B, 3C, 55, 71, 6, 7, 42E, and 73 were mercury-sensitive.

Relation of Mercury Resistance to Epidemic Propensity

Analysis of the relation of mercury resistance to phage-type, discussed in the previous section, showed that the mercury-resistant staphylococci were to be found almost exclusively in phage-groups I and III—the groups mainly implicated in hospital outbreaks, particularly in surgical wards.

Further scrutiny of the mercury resistance of different phage-types would seem to confirm the close relationship between mercury resistance and epidemicity. This is particularly evident in the analysis of group-I strains as shown in table III, where, with one notable exception to be discussed later, the results of the mercury resistance test picked out very clearly the epidemic strains—a point that needs no further elaboration in the light of the world-wide prevalence of type-80 infections during the past few years.

The relationship of mercury resistance to the capacity for epidemic spread in hospitals is less clear-cut in the group-III

TABLE IV—DETAILED RESULTS OF MERCURY-RESISTANCE TESTS ON PHAGE-GROUP II STRAINS

Phage-type	No. of strains	Resistant	Sensitive
3C	4	..	4
55	2	..	2
71	19	3	16
3A/71	1	..	1
3B/3C	1	..	1
3C/55	11	..	11
3C/71	2	..	2
55/71	2	..	2
3B/55/71	2	..	2
3B/3C/55	1	..	1
3C/55/71	4	..	4
3B/3C/55/71	1	..	1
3A/3B/3C/55/71	2	..	2

findings shown in table V. The table shows that strains of types 47/53/75/77 and 77—two important epidemic types (Williams 1959)—were almost all mercury-resistant. Types 75/77 and 77 have certainly been notable epidemic types in the Exeter clinical area, particularly before the advent of type 80 during the summer of 1957.

The low proportion of mercury-resistant strains in the 6/7/47/53/54 subgroup was surprising, as this type was also an epidemic one in previous years in the Exeter area. Further scrutiny of the information available on strains in this subgroup suggests, however, that the mercury-resistant strains may represent an epidemiologically distinct category from the mercury-sensitive ones. Thus, of 8 mercury-resistant strains among the 51 strains in this group on which adequate information was available, 7 were isolated from wounds. Of the 43 mercury-sensitive strains, only 6 were isolated from wounds.

Two phage-types associated with outbreaks of staphylococcal infection in hospitals have, however, proved almost uniformly mercury-sensitive in the present series. These are types 52A/79 and 71. It is particularly interesting, therefore, that both types are also epidemiologically notable in that they alone of all the phage-types associated with outbreaks of staphylococcal infection are associated particularly with maternity hospitals rather than with surgical units. These types are also widespread in the population outside hospitals—type 52A/79 as a cause of boils, and type 71 as the organism causing most cases of impetigo. Possibly, therefore, some additional factor—e.g., the susceptibility of the infant's skin to infection—plays a part in the genesis of maternity-unit outbreaks of infection with these two types.

Williams (1959), in his analysis of epidemic staphylococci based on material examined at Colindale, included in table V of his paper some figures that are comparable with the findings discussed above. His table is based on the distribution of phage-types in a series of 1131 strains, no more than one strain of any one type having come from a single incident. The percentages of the different phage-types that were epidemic in the incidents in question are given in this table, the criterion of epidemicity used for the purpose of the table being causation of three or more infections in the episode concerned. Findings from maternity units and from surgical and other units are tabulated separately. The latter percentages are shown diagrammatically in fig. 3, and below them are plotted against the same phage-type categories the percentages of mercury-resistant strains in the present work. The broad similarity of the two diagrams is

TABLE V—DETAILED RESULTS OF MERCURY-RESISTANCE TESTS ON PHAGE-GROUPS III STRAINS

Phage-type	No. of strains	Resistant	Sensitive
6/7/47/53/54/75 and similar patterns	64	15	49
6/47/53/54 and similar patterns ..	9	5	4
7/47/53/54/75 and similar patterns ..	36	10	26
42E and related patterns	9	..	9
47/53/75/77 and similar patterns ..	8	7	1
53, 53/75/77, 53/77/83	8	5	3
54	1	1	..
75/77	4	4	..
75/83	1	1	..
77	22	20	2
83	9	1	8

evident. The higher percentage of epidemic strains of type 71 in the Colindale figures is based on a total of only 6 strains; this no doubt explains why in the Colindale series this type is credited with almost as high a proportion of epidemic strains in surgical units as type 80—a finding that can scarcely be correct.

Relation of Mercury Resistance to Antibiotic Resistance

As epidemic staphylococci are notoriously prone to be antibiotic-resistant it was not surprising that in the present analysis mercury resistance tended to parallel antibiotic resistance, although the resistance of staphylococci to mercury could not be correlated with resistance to any one antibiotic.

With 159 staphylococcal strains in the present series that were found to fall into phage-groups I or III, the laboratories from which the strains were received recorded unequivocally sensitivity or resistance to one or more of the common antibiotics. These strains are tabulated in table VI according to whether they were sensitive or resistant to penicillin and tetracycline; the proportions in each category that were mercury resistant or sensitive are listed in the table. It will be seen that the proportion of mercury-resistant strains increased from 15·1% in the penicillin- and tetracycline-sensitive group to 43·9% in the penicillin-resistant, tetracycline-sensitive group and to 86·6% in the penicillin-resistant, tetracycline-resistant group.

TABLE VI—RELATIONSHIP BETWEEN MERCURY RESISTANCE AND SENSITIVITY TO PENICILLIN AND TETRACYCLINE IN A SERIES OF 159 STAPHYLOCOCCAL STRAINS

Antibiotic		Total	Mercury test	
Penicillin	Tetracycline		Resistant	Sensitive
Sensitive	Sensitive	33	5 (*15·1%*)	28 (*84·9%*)
Resistant	Sensitive	66	29 (*43·9%*)	37 (*56·1%*)
Resistant	Resistant	60	52 (*86·6%*)	8 (*13·4%*)

TABLE VII—RESULTS OF MERCURY-RESISTANCE TEST, EGG-YOLK REACTION, AND SERUM-OPACITY TEST ON 41 STRAINS

Mercury-resistance test	Egg-yolk reaction	Serum-opacity test	No. of strains
+	+	−	6
+	−	+	1
+	−	−	6
−	+	−	21
−	−	+	2
−	−	−	5
		Total ..	41

The results of antibiotic-sensitivity tests on strains falling into the different phage-types confirmed that mercury resistance did not parallel antibiotic resistance precisely—e.g., 46 type-80 strains, all mercury-resistant, were included in the 159 above-mentioned. They comprised 4 strains that were sensitive to penicillin and tetracycline, 11 penicillin-resistant, tetracycline-sensitive strains and 31 strains that were resistant to both penicillin and tetracycline.

A small series of 5 type-80 strains, received more recently from a mental hospital and not included in the series discussed hitherto, demonstrated quite clearly that mercury resistance and antibiotic resistance were independent properties. Thus, 2 of the 5 strains were mercury-resistant and 3 mercury-sensitive. 1 mercury-sensitive strain was penicillin- and tetracycline-sensitive, 2 sensitive strains were penicillin-resistant, tetracycline-sensitive. Of the 2 mercury-resistant strains, 1 was resistant to penicillin and sensitive to tetracycline and the other resistant to both penicillin and tetracycline.

These findings are compatible with the view that the mercury-resistance test distinguishes two broad groups of staphylococci, and that the mercury-resistant group is more prone to become resistant to antibiotics than the mercury-sensitive one.

Relation of Mercury Resistance to Other Properties of Staphylococcal Strains.

A small series of strains was examined by the eggyolk reaction (Gillespie and Alder 1952), by the serum-opacity test of Tomlinson and Parker (1956), and by the mercury-resistance test. No relationship was found between mercury resistance and the findings with the other two tests. The different combinations of results found in the three tests on a total of 41 strains are summarised in table VII.

Discussion

As an empirical aid in routine bacteriological work, a new selective medium requires no further justification than that it should increase the frequency of isolation of the organism for which it has been devised. Judged on this level alone, the mercuric chloride agar described here should be useful. In the isolation of type-80 staphylococci, for example, from wards where infections due to this organism are occurring, the mercury medium with added milk has already proved very effective—partly because of the distinctive appearance of *Staph. aureus* colonies, partly by the suppression of many of the saprophytic organisms from ward dust, and also by the inhibition of swarming of proteus.

Unlike other selective media, however, mercuric chloride agar appears to pick out organisms for the rapid recognition of which no other laboratory test is at present available—namely, those staphylococci that tend to give rise to outbreaks of staphylococcal infection in hospitals. The mercury-resistance test may therefore prove useful as a rapid screen test for epidemic staphylococci in hospital laboratories, particularly where phage-typing is not readily obtainable. The test should also be useful in the day-to-day control of infections on the time-honoured basis of rapid recognition and segregation of sources of infection in the population concerned. Preliminary experience of the results of segregating infected patients on this basis has been very encouraging. The presumption that mercury-sensitive staphylococci are of no epidemiological moment would of course be quite unjustified on the evidence cited above, least of all in maternity-nursery outbreaks. But any test which rapidly picks out at least the great majority of the major hospital staphylococcal pathogens within twenty-four hours would seem worth using for day-to-day control until some less empirical method is discovered. The test can, of course, be used in maternity-unit outbreaks in which type-80 or some other mercury-resistant type is concerned.

Virtually nothing seems to be known about the mechanism of selective action of metals on different bacterial groups, and with most selective media this matters little if the medium is effective in practice. It is tempting to speculate, however, on the possible relationship of mercury resistance to the observed behaviour of the epidemic staphylococci in hospitals. Three obvious possibilities come to mind. First, mercury resistance may not be directly related in any way to the mechanisms underlying the pathogenicity of the epidemic staphylococci; or at most this resistance might be one indication of a greater versatility of these strains in different environments. Their proneness to antibiotic resistance could then be cited as further evidence of this versatility. Raffel (e.g., Uyeda and Raffel 1959) has suggested that the pathogenicity of the tubercle bacillus to man, in contrast with that of other mycobacteria, may be at least partly explained in this way.

The circumstance in which the differential activity of mercury was first observed raises the second possibility—that staphylococci that happened to be mercury-resistant have acquired, by passage in hospital patients, an enhanced virulence through their ability to multiply in vivo in the vicinity of a foreign body such as catgut impregnated with

mercuric salts. Such a suggestion would fail to account for the differential mercury resistance itself, and for the capacity of the same strains to become resistant to antibiotics. Moreover, the sudden emergence of the type-80 staphylococcus as a major pathogen in so many countries in the early 1950s seems very difficult to explain on this basis. Nevertheless, experiments are now in progress in which surgical wounds are being sutured with alternate sutures of two selected batches of suture material, with and without a sufficient concentration of mercuric salts to give in-vitro results similar to those obtained in our early experiments. A study of the bacteria that multiply in the neighbourhood of these different sutures in the wounds of individual patients may throw some light on the possible selection of mercury-resistant staphylococci in this way.

Finally, it is possible that certain staphylococcal strains, endowed with hitherto undiscovered antigenic or metabolic characters that make them potentially epidemic, are, because of these characters, also more resistant to mercury than other staphylococci. It would be wrong to suppose that the epidemic staphylococci are necessarily more virulent than the non-epidemic types in the sense that, once introduced into the body, they either produce more or more potent toxins than other strains, or can multiply from smaller inocula. The difference might be one of greater "communicability". As has been mentioned, some coagulase-negative skin staphylococci are mercury-resistant by the test described in this paper. Lepper (1958) reported that, in a number of hospital surveys, the coagulase-negative skin staphylococci appeared to become antibiotic-resistant more readily than coagulase-positive strains, and that, by the marker characteristic of antibiotic resistance, these strains also spread more rapidly through hospital wards than the pathogenic staphylococci. The property of high communicability might explain not only the prevalence of infection with the epidemic staphylococci but also their greater resistance to antibiotics, as such strains would be more frequently present in environments favouring the emergence of resistant variants.

Fildes (1940) was the first to suggest that mercury acted on bacteria by combining with —SH groups. A direct comparison of epidemic and non-epidemic staphylococci with this in mind might perhaps throw new light on the metabolic or other properties that confer epidemic propensities on some staphylococci such as type 80. Given, however, the large number of bacterial enzymes known to be inhibited by mercury, such an undertaking might be extremely complex.

Whether the phenomenon of mercury resistance offers a reliable prognostic guide to the epidemic capacities of a given staphylococcal strain, or is directly or indirectly related to its virulence, are questions that only much wider experience of the test may eventually elucidate.

Summary

Staphylococci of phage-types known to be associated with epidemic hospital infection, particularly in surgical units, were found to be more resistant to mercuric salts than non-epidemic strains.

A series of 505 staphylococcal strains received for phage-typing from various laboratories in the South-west of England were divided into mercury-resistant and mercury-sensitive groups on the basis of growth or absence of growth on peptone agar containing 1 in 27,500 mercuric chloride.

In a series of 210 staphylococci falling into phage-group I, 137 (95·1%) out of 144 strains of phage-types 80 or 52/52A/80 were mercury-resistant. Phage-group I strains without an "80" in their phage pattern were all mercury-sensitive. Only 3 (5·9%) out of 52 phage-group II strains were mercury-resistant; all 3 were type-71 strains isolated from wounds. Of 171 group-III strains, 69 (40·0%) were mercury-resistant. The mercury-resistant strains in this group appeared to belong mainly to phage-types associated with epidemic infection.

The property of mercury resistance paralleled in general that of antibiotic resistance. In a series of 159 strains, falling into phage-groups I or III, whose sensitivity to penicillin and tetracycline had been recorded, 5 (15·1%) out of 33 strains sensitive to both antibiotics were mercury-resistant, compared with 52 (86·6%) out of 60 strains resistant to both penicillin and tetracycline. Of 60 strains resistant to penicillin but sensitive to tetracycline, 29 (43·9%) were mercury-resistant.

The results of mercury-resistance tests showed no correlation with those of the egg-yolk reaction or the serum-opacity test.

The use of the mercury-resistance test as a rapid presumptive test for epidemic staphylococci and in day-to-day control of hospital infection is discussed.

I am grateful to Mr. A. M. N. Gardner, control-of-infection officer at the Torbay Hospital, for his stimulating collaboration in a long-term study of infection in that hospital. The present paper arose indirectly from one of many discussions with Mr. Gardner; a detailed epidemiological and bacteriological account of the Torbay Hospital studies will be published later in a joint paper. I am also grateful to the South West Regional Hospital Board for a research grant; to Sister E. M. Cottrell, who has given invaluable help in our epidemiological studies; and to my technician, Mr. H. E. Gay, for his enthusiastic technical assistance.

REFERENCES

Asheshov, E. H., Rippon, J. E. (1959) *J. gen. Microbiol.* **20**, 634.
Carroll, B. (1955) *J. Bact.* **69**, 413.
Fildes, P. (1940) *Brit. J. exp. Path.* **21**, 67.
Gillespie, W. A., Alder, V. G. (1952) *J. Path. Bact.* **64**, 187.
— Pope, R. C., Simpson, K. (1957) *Brit. med. J.* i, 1044.
Lepper, M. (1958) National Conference on Hospital-Acquired Staphylococcal Disease; p. 55. U.S. Department of Health, Education, and Welfare. Atlanta, Georgia.
Parker, M. T., Tomlinson, A. J. H., Williams, R. E. O. (1955) *J. Hyg., Camb.* **53**, 458.
Rountree, P. M. (1959) *J. gen. Microbiol.* **20**, 620.
Tomlinson, A. J. H., Parker, M. T. (1956) *Nature, Lond.* **117**, 895.
Uyeda, C. T., Raffel, S. (1959) *Amer. Rev. resp. Dis.* **80**, 849.
Williams, R. E. O. (1959) *Lancet*, i, 190.
— Rippon, J. E. (1952) *J. Hyg. Camb.* **50**, 320.

CEREBRAL MANIFESTATIONS OF ADDISONIAN PERNICIOUS ANÆMIA

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THE association of neurological lesions with Addisonian pernicious anæmia has been recognised for many years, and the term "subacute combined degeneration" has long been in use to describe these nervous manifestations, which may sometimes antedate the blood changes. This term tends to be misleading as it does not take cognisance of the fact that, in addition to the spinal and peripheral nerve lesions, the brain may also be affected. That mental changes do occur not uncommonly, with or without spinal involvement, has been known for over 50 years. Indeed, Addison in his original description of pernicious anæmia in 1855 noted that the mind occasionally wandered. Langdon (1905) described a group of cases in which nervous and mental symptoms, such as gradual mental deterioration, made their appearance in what he called the "pre-pernicious anæmia" phase.

McAlpine (1929) reported mental changes, varying from

states of depression with loss of mental energy to definite psychoses, often preceding the blood changes by many months. Holmes (1956) described the mental symptoms in fourteen personal cases, and found them to be extremely variable, ranging from mild disorders of mood to severe dementia. In one case the cerebral symptoms had first appeared 8 years before the onset of anæmia or other neurological signs, and two patients had received courses of electric convulsion therapy. More recently, Weiner and Hope (1959) reported the case-history of a 44-year-old woman who had such severe paranoid symptoms that she required institutional care, and was given electric-shock treatment. Later, as the result of vitamin-B_{12} therapy, she made a complete mental recovery.

The following case-history of a woman, who received a course of electric convulsion therapy, is presented for two main reasons: (1) to draw attention once more to the mental changes which may accompany or precede Addisonian anæmia, and (2) to show how complete recovery may result from adequate treatment with vitimin B_{12}.

Case-report

The patient, aged 58, was admitted to this infirmary on Oct. 21, 1959. Her symptoms had begun 4 years previously when she became depressed and tense, and suffered from headaches and insomnia. At that time she was seen by a psychiatrist and was reported as having an endogenous depression. Electric convulsion therapy was suggested but refused. Her symptoms slowly progressed, and she was admitted to a mental institution as a voluntary patient in May, 1959. She was given six electric convulsion treatments without beneficial effect. A blood examination was not carried out. 6 weeks before her admission to this infirmary she became exhausted and very breathless, and developed œdema.

She was a stout and very pale woman—listless, depressed, and withdrawn. Numerous bruises and marked ankle œdema were present. Tongue smooth. No splenic enlargement. No evidence of subacute combined degeneration of the cord. Blood examination: hæmoglobin, 13%; packed-cell volume, 6·5%; mean corpuscular hæmoglobin concentration (M.C.H.C.), 30%; erythrocyte-sedimentation rate (Westergren), 25 mm. in first hour; reticulocyte-count less than 2%. Blood-film showed a very severe macrocytic anæmia with hæmoglobinised megaloblasts and hypersegmented polymorphs. Histamine test-meal revealed no free acid.

On Oct. 22 treatment with vitamin B_{12} was commenced with an initial dose of 1000 μg. by injection, followed by 250 μg. twice weekly. In addition, she received five pints of blood by transfusion during the first week. On Oct. 30 the hæmoglobin was 44%; packed-cell volume, 23%; M.C.H.C., 27%; reticulocyte-count, 16%. Oral iron therapy was added.

She showed a dramatic clinical improvement and came to life again, becoming more alert, sitting up and taking an interest in the activities of the ward. Headaches were much less severe. When discharged from hospital on Nov. 13 she was up and about and mentally much brighter. Hæmoglobin, 65%; packed-cell volume, 31%; M.C.H.C., 31%; erythrocyte-sedimentation rate, 8 mm. in first hour.

When last seen on Jan. 7 she looked the picture of health. According to her husband she was her old cheery self again, and was once more "livable with". She no longer felt depressed, and had resumed her social activities. Hæmoglobin, 93%; packed-cell volume, 43%; M.C.H.C., 33%.

Discussion

The cerebral lesions in vitamin-B_{12} deficiency seem to be essentially the same as those found in the cord, and consist of more or less diffuse, but uneven, degeneration of the white matter with relatively little proliferation of the fibrous glia (Woltman 1918, Adams and Kubik 1944, Holmes 1956). Woltman was also able to demonstrate focal lesions in the grey matter with destruction of some of the pyramidal cells, but Adams and Kubik and Holmes did not find any specific changes in the nerve-cells. This degenerative process appears to be related to a decrease in cerebral metabolism, the result of the vitamin-B_{12} deficiency, and not to the anæmia. This was shown by Scheinberg (1951) who estimated the cerebral blood-flow and oxygen consumption by the nitrous-oxide method. He also found electroencephalographic abnormalities which improved with treatment.

When mental symptoms occur in conjunction with the classical picture of Addisonian anæmia or subacute combined degeneration, the diagnosis is not usually in doubt. Difficulty arises, however, when the mental symptoms are prominent and the usual diagnostic criteria are slight or absent. As the reversibility of these symptoms largely depends on their duration (McAlpine 1929, Holmes 1956), the importance of early diagnosis and prompt treatment, if it is to be effective, is obvious.

How, then, can an early diagnosis be established before irreversible cerebral damage has taken place? Clearly, textbooks should draw attention to the possibility of mental changes occurring as part of the clinical picture of Addisonian anæmia. More positive action could be taken along the lines suggested in 1929, by McAlpine, who recommended that patients over the age of 35 with primary neurosis and psychoses should have frequent examination of the blood and gastric contents. Holmes (1956) felt that, in such cases with normal cell-counts in blood and marrow, and indefinite neurological signs, use should be made of such medical procedures as gastric biopsy, estimation of serum-B_{12}, electroencephalography, and muscle biopsy. By such measures the number of patients with irreversible mental changes would be considerably reduced.

It is now generally accepted that much larger doses of vitamin B_{12} are required for the treatment of subacute combined degeneration of the cord than for uncomplicated Addisonian anæmia. In the same way, patients with mental symptoms must be given large amounts of vitamin B_{12}. Holmes suggests an initial dose of 1000 μg., followed by 500 μg. twice weekly for the first month, and thereafter not less than 100 μg. weekly for the next 6 months.

Summary

The case of a woman in whom cerebral symptoms were associated with Addisonian anæmia is reported.

The mental changes, which appeared four years before the anæmia became manifest, were thought to be due to an endogenous depression, and she was given a course of electric convulsion therapy without effect.

She made a complete recovery after vitamin-B_{12} therapy.

As the reversibility of the mental symptoms depends to a large extent on their duration, the importance of early diagnosis and prompt treatment is obvious. Early diagnosis depends primarily on the physician's awareness of the existence of cerebral changes in Addisonian anæmia.

My thanks are due to Dr. H. E. Hutchison, of the hæmatological department, for laboratory reports.

REFERENCES

Adams, R. D., Kubik, C. S. (1944) *New Engl. J. Med.* **231**, 1.
Addison, T. (1868) Dr. Addison's Works; p. 213. New Sydenham Society.
Holmes, J. M. (1956) *Brit. med. J.* ii, 1394.
Langdon, F. W. (1905) *J. Amer. med. Ass.* **45**, 1635.
McAlpine, D. (1929) *Lancet*, ii, 643.
Scheinberg, P. (1951) *Blood*, **6**, 213.
Weiner, J. S., Hope, J. M. (1959) *J. Amer. med. Ass.* **170**, 1038.
Woltman, H. W. (1918). *Arch. intern. Med.* **21**, 791.

SHIGELLOSIS AND SULPHONAMIDES

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SHIGELLOSIS, even when it occurs as epidemic acute dysentery, is not a disease in which clinical assessment of treatments is easy. Many of the problems are illustrated in papers by Taylor (1959) and by Falisevac et al. (1959) concerning streptomycin-sulphonamide combinations. Varying bacterial species or types; varying intervals from onset of illness to beginning of treatment; varying kinds of patients (e.g., from healthy adults to malnourished infants); and the frequency of rapid spontaneous cure—all these combine to confuse the analysis of figures. The situation is further obscured when, as in Jamaica, sporadic rather than epidemic incidence makes consistent therapy hard to organise; the presenting symptom is not always dysentery; and bacteriological follow-up is impaired by the impossibility of retaining symptomless patients in urgently needed beds and by the near-impossibility of persuading these same patients or their parents to bring specimens to the hospital once they have been discharged.

In the absence of an adequately controlled trial in his own land, the clinician must rely upon his own and his colleagues' impressions, or upon laboratory findings, to indicate whether changes noted elsewhere are occurring around him. The general clinical impression prevailing in the University College Hospital of the West Indies in 1958 was that sulphonamides were still effective against shigellosis here. I decided to check this impression by in-vitro studies of the shigella strains which had been isolated during that year.

Bacteriological Investigation

Shigellæ were isolated from 44 patients. No patient was found to have more than one strain. 40 strains were available for study (24 of *Sh. sonnei*, 2 of *Sh. flexneri 1*, 9 of *Sh. flexneri 3*, and 5 of *Sh. flexneri 6*). In each case, the isolate studied was obtained from a specimen passed before any specific therapy had been given in hospital, except that one patient was already receiving streptomycin for a tuberculous infection. So far as could be determined, no patient had received antibacterial drugs for the illness in question before reporting to the hospital.

An unexplained feature of the cases studied here is their age-distribution—23 under 5 years of age (16 *Sh. sonnei* and 7 *Sh. flexneri*) and 15 over the age of 18 (8 *Sh. sonnei* and 7 *Sh. flexneri*) but none between the ages of 5 and 18.

Methods

Strains, maintained on egg-medium slants, were subcultured to MacConkey's agar and purified if necessary. Tryptose-broth (' Difco ') cultures were then set up.

Sulphonamide-sensitivity determinations were carried out in the sulphonamide-antagonist-free broth described by Jewell and Pearmain (1954). Each organism was inoculated into 3 ml. volumes of broth alone, of broth containing 100 μg. of sulphadimidine per ml., and of broth containing 500 μg. per ml. Size of inoculum is critically important in determining sulphonamide sensitivities (Fleming 1940, Colebrook and Francis 1941). Inocula usually consisted of single drops from Pasteur pipettes (approximately " 50-dropper ") of 1/100 dilutions of four-hour broth cultures. A few of the *Sh. sonnei* strains persistently grew poorly in the tryptose broth and failed to grow at all from such small transfers. These were retested with heavier inocula, not exceeding 1 drop of a 1/10 dilution of the tryptose broth culture. Absence of visible growth in a sulphonamide-containing tube after eighteen hours' incubation at 37°C was taken as indicating sensitivity of the organism, provided that growth had occurred in the control tube.

Laboratory Results

Shigella sonnei.—22 of the 24 strains were resistant to 100 μg. of sulphadimidine per ml.—which is higher than levels usually obtained in blood—and 16 of these were resistant to 500 μg. Only 2 strains, therefore, were found to be sensitive to a level suggesting the possibility of successful sulphonamide therapy.

Shigella flexneri.—All 16 strains were sensitive to 100 μg. of sulphadimidine per ml.

Clinical Histories

Hospital notes were available for all the patients except 2 of those with *Sh. flexneri* infections. Because of the strikingly different in-vitro sulphonamide sensitivities of the *Sh. sonnei* and the *Sh. flexneri* strains, the two groups of patients will be reviewed separately.

Sonne infections (24)

Of 4 infants desperately ill on admission, 3 died within a few hours. The 4th made a dramatic recovery on treatment with tetracycline and cortisone. They can therefore be ignored in assessing the value of sulphonamide therapy.

12 of the 20 mild cases were treated with sulphonamides, 9 of them, so treated before the bacteriological findings were known, made rapid recoveries. The 10th received sulphonamide therapy for a week with good clinical response, but was still excreting *Sh. sonnei* until she was given a course of tetracycline. Her strain was sensitive to 500 μg. of sulphadimidine per ml. but not to 100 μg. One adult developed dysentery in hospital, made a spontaneous recovery in twenty-four hours, and only received sulphonamide after isolation of the organism had been reported. The remaining sulphonamide-treated patient had had dysentery for six days and was already recovering before she reported sick. She continued to improve slowly during five days of sulphonamide therapy.

One adult who developed dysentery shortly after admission received no specific treatment. She recovered completely in two days.

The remaining 7 patients made rapid and uneventful recoveries on streptomycin, tetracycline, or chloramphenicol.

Flexner infections (14)

1 infant, seriously ill and malnourished on admission, died before adequate therapy could be given. A 2nd seriously ill infant, treated with chloramphenicol, died three days after admission from bronchopneumonia.

Of 5 other children under 4 years of age, 1, given sulphonamide as an outpatient, failed to return to hospital—probably an indication of successful treatment. 3 were treated with chloramphenicol and 1 with streptomycin. All made rapid clinical recoveries.

Of 5 adults treated with sulphonamides, 4 recovered rapidly; 1, treated with sulphonamide as an outpatient, failed to return. The 2 remaining adults were treated with antibiotics. One was already improving before starting tetracycline. The other made a slow clinical recovery on chloramphenicol, but was still excreting *Sh. flexneri* eight days after the beginning of treatment (see below).

From this retrospective survey of the records of a small number of variously treated patients, it is clearly impossible to draw any positive conclusions as to the efficacy of sulphonamide therapy, especially as bacteriological follow-up was nearly always inadequate to prove elimination of infection. The most that can be said is that the clinical data do not give grounds for doubting the relevance of the laboratory findings.

Note on Antibiotic Sensitivities

At the time of sulphonamide-sensitivity testing, all strains were tested on blood-agar plates for sensitivity to discs of streptomycin (10 μg.), tetracycline (5 μg.), and chloramphenicol (5 μg.). 16 of the 24 *Sh. sonnei* strains and all the *Sh. flexneri* strains were fully sensitive to all three antibiotics. 7 *Sh. sonnei* strains showed resistance or reduced sensitivity to streptomycin or tetracycline or both. The only chloramphenicol-resistant strain, which was also streptomycin-resistant, was isolated from a patient who developed dysentery while already receiving streptomycin for a pleural effusion. No record was found of her ever having received chloramphenicol.

Reading of the history of the patient who was still excreting *Sh. flexneri* eight days after beginning chloramphenicol treatment prompted examination of his post-treatment isolate. Plate-disc testing showed it to be sensitive to tetracycline but resistant to streptomycin and to chloramphenicol. By a broth-dilution technique similar to that employed for the sulphonamide sensitivity determinations, it was found (using doubling dilutions) to be inhibited by 1 μg. of tetracycline but only by 64 μg. of streptomycin and by 128 μg. of chloramphenicol. Unfortunately, the pre-treatment isolate, which had shown sensitivity to all three antibiotics on plate-disc testing, was no longer available for quantitative testing. But it appears that this patient's unsatisfactory response to chloramphenicol was associated with the emergence of the only antibiotic-resistant *Sh. flexneri* strain found in the present series, and that this resistance involved streptomycin, which the patient had not received, as well as chloramphenicol.

Discussion

Hardy (1945) reported the ready development of sulphonamide-resistance by *Sh. sonnei* strains in New York State in 1943. Since then, similar reports, involving shigellæ of all types, have come from many parts of the world (e.g., Cheever 1946, Philippine Islands; Tateno 1950, Japan; Garfinkel et al. 1953, Korea; Davies 1954, London; Verselder et al. 1655, Belgian Congo; Marberg et al. 1958, Israel; Stein and Schaff 1958, South Africa). It seems that the time is approaching when sulphonamides will cease to be effective against shigellosis. Yet clearly this time must be delayed as long as possible, especially as many recent reports also refer to the emergence of antibiotic-resistant shigella strains. Both Marberg et al. (1958) from Israel, and Olarte and De La Torre (1959) from Mexico, provide evidence of disturbingly rapid adaptation of shigella populations to changes in prevailing therapy. Marberg et al. comment: " Bacillary dysentery, after having been almost deleted as a problem with important clinical implications, may revert to its former clinical severity, thus demanding again new means of therapy."

How can we make the best use of our available means? Possibly by adopting the following lines of policy:

1. Many mild cases do not need specific antibacterial therapy, and, by withholding it until it is plain that spontaneous cure is not taking place, the time may be deferred when severe cases due to untreatable organisms make their appearance.

2. While spontaneous cure is awaited, the sensitivity pattern of the infecting organism should be determined, so that, if antibacterial therapy is used, it may be well directed and adequate.

3. When such cases are treated, it is probably preferable to use sulphonamides against strains that are still sensitive to them—e.g., the Jamaican *Sh. flexneri* strains. This suggestion is subject to the qualification that combination-therapy may be shown to prevent the emergence of resistant strains. Even if this is so, it will presumably necessitate the use of two agents to which the infecting organism is known to be sensitive, rather than predetermined mixtures such as those employed by Taylor (1959) and by Falisevac et al. (1959).

4. Treatment of severe cases must, of course, precede isolation of the organism, and must therefore at first be guided by general knowledge of the strains prevailing in the area at the time.

5. The importance of public-health measures and personal hygiene is self-evident.

Summary

Shigellosis occurs in Jamaica as a sporadic endemic infection of varied presentation and severity, and thus does not lend itself to controlled trials of therapy.

In the laboratory, 22 of 24 *Sh. sonnei* strains isolated at the University College Hospital of the West Indies during 1958 were sulphonamide-resistant, whereas all of 16 *Sh. flexneri* strains were sulphonamide-sensitive.

Retrospective examination of the patients' clinical records threw very little light upon the clinical efficacy of sulphonamides against the two types of infection.

Suggestions regarding treatment are made in the light of the world-wide increase in shigella strains resistant to sulphonamides and to antibiotics.

My thanks are due to Miss Marjorie Sanguinetti, D.S.M.T., for the isolation and identification of the shigella strains studied; and to Dr. E. H. Back, consultant pædiatrician to the University College Hospital of the West Indies, and to other clinical colleagues, for access to clinical records.

REFERENCES

Cheever F. S. (1946) *U.S. nav. med. Bull.* **46**, 479.
Colebrook, L., Francis, A. E. (1941) *J. Path. Bact.* **53**, 155.
Davies, J. R. (1954) *Mon. Bull. Min. Hlth Lab. Serv.* **13**, 114.
Falisevac, J., Kosutic, Z., Galinovac-Weisglass, M. (1959) *Brit. med. J.* ii, 12.
Fleming, A. (1940) *J. Path. Bact.* **50**, 69.
Garfinkel, B. T., Martin, G. M., Watt, J., Payne, F. J., Mason, R. P., Hardy, A. V. (1953) *J. Amer. med. Ass.* **151**, 1157.
Hardy, A. V. (1945) *Publ. Hlth Rep., Wash.* **60**, 1037.
Jewell, P., Pearmain, G. E. G. (1954) *J. clin. Path.* **7**, 308.
Marberg, K., Altmann, G., Eshkol-Bruck, A. (1958) *Amer. J. trop. Med. Hyg.* **7**, 51.
Olarte, J., De La Torre, J. A. (1959) *ibid.* **8**, 324.
Stein, H., Schaff, G. (1958) *S. Afr. med. J.* **32**, 1161.
Tateno, I. (1950) *Jap. J. exp. Med.* **20**, 795.
Taylor, P. J. (1959) *Brit. med. J.* ii, 9.
Verselder, R., Courtois. G., Limbo, P. (1955) *Bull. Soc. Path. exot.* **48**, 892.

DETECTION OF PREDIABETES BY GLUCOSE-TOLERANCE TEST SENSITISED BY PREDNISOLONE *

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THE glucose-tolerance test has proved to be the best means of detecting early or mild diabetes mellitus. If the disease can be detected in an early or presymptomatic stage, it may be controllable by diet. But in borderline cases where the tolerance test reveals some abnormality yet does not satisfy all the criteria for diabetes mellitus repeated tests and observation of the clinical course are sometimes required before one can decide whether the prediabetes state exists.

If a person has a latent impairment of carbohydrate metabolism, this may be made manifest by administration of diabetogenic substances. This was suggested by Zucker (1949) and its application was studied by Berger (1952) with corticotrophin, and by Fajans and Conn (1954) and others (Downie 1955, West 1957, German 1958, Goudie et al. 1958, Duncan 1956) with corticosteroids. The present study was undertaken to ascertain

* The data of this paper were presented to the Japanese Society of Endocrinology on April 2, 1957, and to the Japanese Diabetes Society in April, 1958.

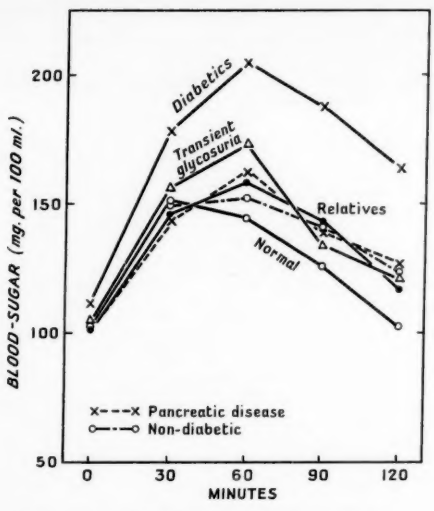

Fig. 1—Mean standard glucose-tolerance curves.

whether the prediabetic state can be demonstrated by the glucose-tolerance test sensitised with prednisolone.

Materials and Method

The subjects were 10 healthy adults (average age 27), 14 non-diabetic patients with various non-febrile diseases (35 years old), 9 patients with pancreatic disease of varying ætiology (44 years old), 3 patients with a recent history of undetermined transient glycosuria (46 years old), 17 healthy persons with a family history of diabetes mellitus (24 years old), and 20 patients with diabetes mellitus (48 years old).

After an overnight fast, 50 g. of glucose dissolved in 250 ml. of water was administered orally. Capillary blood was collected from the ear-lobe in the fasting state and every thirty minutes for two or three hours after the ingestion of glucose. Urine specimens were collected every hour. Within three days, the test was repeated in the same way except that 10 mg. of prednisolone was given two hours before the glucose. Each subject had been on a diet containing at least 300 g. of carbohydrate daily for three days before the test. In diabetics this study was performed usually before initiating insulin treatment or after omission of regular insulin for twenty-four hours. Our diet for diabetics consisted of 300 g. of carbohydrate, 30–50 g. of fat, and 70–100 g. of protein daily. Blood-sugars were determined by the method of Fujita and Iwatake (1931). According to our unpublished study, this gives the same values as that of Hagedorn and Jensen (1923).

The diagnosis of chronic pancreatitis and cancer of the pancreas were made after X-ray examinations, analysis of duodenal juice, and determination of serum-amylase levels after subcutaneous injection of neostigmine (Knight et al. 1949, Yamagata et al. 1956).

Interpretation of Glucose-tolerance Test

We performed the standard glucose-tolerance test on 54 non-diabetic control subjects, 6 renal-glycosuric patients, and 76 diabetic patients, as reported previously (Goto et al. 1957). Our standards for the capillary blood-sugar glucose-tolerance test are:

Normal.—Fasting not exceeding 120 mg. per 100 ml., peak not exceeding 200 mg.; two hours not exceeding 120 mg.; no glycosuria at any time.

Diabetic.—Peak more than 200 mg. per 100 ml., at two hours more than 140 mg. and glycosuria; if urine sugar free, masked diabetes or diabetes with high renal threshold.

TABLE I

Group	No.	Test	Findings of test: Normal	Findings of test: Uncertain abnormalities	Findings of test: Diabetic	Positivity of prednisolone test (%)
Normal	10	S	9	1	0	
		P	9	1	0	0
Non-diabetic patients	14	S	6	8	0	
		P	6	7	1	7
Relatives of diabetics	17	S	6	11	0	
		P	3	8	6	35
Pancreatic disease	9	S	4	4	1	
		P	1	4	4	44
Transient glycosuria	3	S	1	2	0	
		P	0	1	2	67
Diabetic patients	20	S	0	5	15	
		P	0	0	20	100

S=standard glucose-tolerance test. P=prednisolone glucose-tolerance test.

Uncertain abnormalities.—(*a*) Fasting above 120 mg. per 100 ml., but peak and two-hour values within normal range; (*b*) peak over 200 mg. but not exceeding 230 mg. with normal fasting and two-hour values, with or without glycosuria; and (*c*) two-hour value over 120 mg. per 100 ml., but normal fasting and peak values and no glycosuria (delayed hyperglycæmia).

Our criteria for a positive prednisolone glucose-tolerance test are a peak of more than 200 mg. per 100 ml., a two-hour level of more than 140 mg., and glycosuria. If the urine is sugar-free, we still interpret the test as positive.

As a means of recording the blood-sugar response to prednisolone, we calculated the sum of the differences of blood-sugar values in the standard glucose-tolerance curve and the prednisolone glucose-tolerance curve at each time-point and represented this sum as the *response index*. The changes in arteriovenous blood-sugar differences after glucose ingestion have been reported (Goto et al. 1959).

Results

The results are summarised in table I and figs. 1 and 2. In the standard glucose-tolerance test the mean blood-sugar curves of the normal group, the non-diabetic patients' group, the relatives' group, and the pancreatic-disease group are close to one another (fig. 1), but in the prednisolone glucose-tolerance test they are separate (fig. 2).

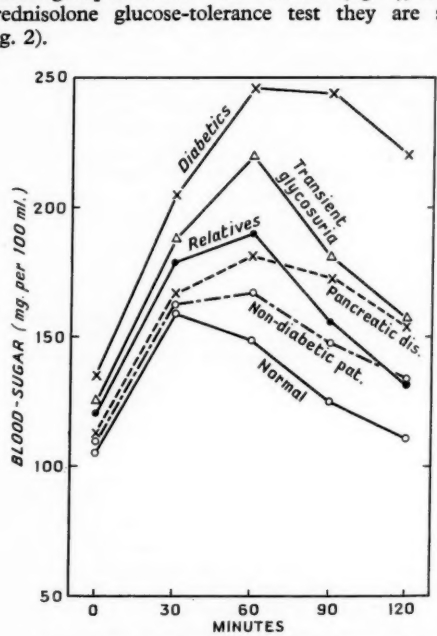

Fig. 2—Mean prednisolone glucose-tolerance curves.

TABLE II—CASES WITH A HISTORY OF TRANSIENT GLYCOSURIA

No.	Age and sex	Standard glucose-tolerance test: Blood-sugar (mg. per 100 ml.) Fast	½	1	1½	2	3	Urine sugar	Prednisolone glucose-tolerance test: Blood-sugar (mg. per 100 ml.) Fast	½	1	1½	2	3	Urine sugar
1	48 M	106	163	160	151	144	68	−	137	186	196	151	137	87	−
2	36 F	104	157	170	106	92	..	−	117	168	207	174	140	..	+
3	53 F	94	151	193	146	130	..	−	124	215	261	215	191	..	+

TABLE III—MEAN BLOOD-SUGAR DIFFERENCE BETWEEN STANDARD GLUCOSE-TOLERANCE TEST AND PREDNISOLONE GLUCOSE-TOLERANCE TEST

Group	No.	Blood-sugar (mg. per 100 ml.)* Fasting	Peak	Two-hour
Normal subjects ..	10	−0·9±2·4	3·4±4·8	5·5±3·5
Non-diabetic patients ..	14	7·8±3·0	14·1±4·4	9·4±9·2
Relatives of diabetics ..	17	19·0±5·3	33·4±6·7	14·0±4·5
Pancreatic disease ..	9	10·6±4·8	28·0±6·3	29·7±7·6
Diabetic patients ..	20	25·0±6·7	47·2±9·3	45·7±8·5

* Mean ± standard error.

The *normal* group revealed little or no change in the glucose-tolerance curve after pretreatment with prednisolone.

Of the 14 *non-diabetic* patients, 8 had two-hour values of more than 120 mg. per 100 ml., with normal peak values, in the standard test. In the prednisolone glucose-tolerance test 1 of these, a 15-year-old girl with Graves' disease, showed a diabetic curve.

Of the 17 *relatives* 11 had two-hour values of more than 120 mg., with normal peak values. In the prednisolone glucose-tolerance test; 6 (35%) showed a diabetic curve, and the test was normal in only 3. Fig. 3 compares the curves of the normal group and the relatives' group.

Of the 6 patients with chronic *pancreatitis*, whose standard glucose-tolerance test were normal, 2 showed a diabetic curve in the prednisolone glucose-tolerance test. Both of the patients with *pancreatic cancer* (1 of whom had a diabetic standard-glucose-tolerance test) had a positive prednisolone glucose tolerance test.

The results of the prednisolone glucose-tolerance test in the 3 patients with a recent history of transient *glycosuria* of unknown origin but without an evident family history of diabetes mellitus are shown in table II. 2 of the 3 (1 of whom had a normal standard glucose-tolerance test) showed diabetic curves with glycosuria. This fact is worth noting, because a person who has had transient glycosuria sometimes shows a quite normal glucose-tolerance test or a borderline test without glycosuria. Such cases have been called normal or at least non-diabetic. On the prednisolone glucose-tolerance test, these 2 cases could be classified as prediabetes.

The 20 *diabetic* patients studied were mild and non-ketotic.

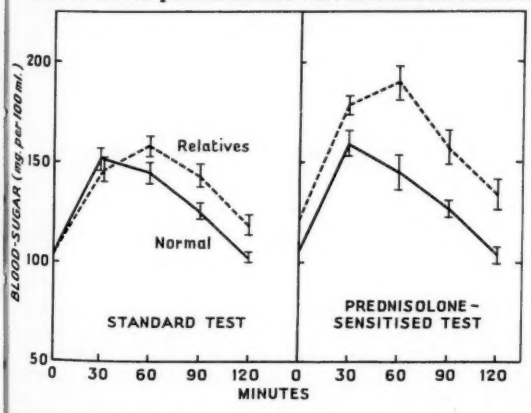

Fig. 3—Comparison of mean glucose-tolerance curves of normal group and of relatives-of-diabetics group. Vertical bars represent standard errors.

13 had a normal fasting blood-sugar and 5 failed to satisfy the criteria for diabetes with the standard glucose-tolerance test. These 5 were in remission, or improved by diet, at the time of the study. In the prednisolone glucose-tolerance test all the cases showed typical diabetic curves.

To see at what point in the tolerance curve blood-sugar is most influenced by pretreatment with prednisolone, the mean blood-sugar differences between the standard test and the prednisolone test were calculated (table III). In the normal group, little change was noted in the peak and the two-hour values, and little or no change was seen in the fasting. The striking changes in the relatives' group are the increase in the peak and the fasting levels with a relatively slight increase in the two-hour values. In the patients with pancreatic disease, the peak and two-hour values increased markedly after pretreatment with prednisolone, though the increase in the fasting level was relatively small. In the diabetics, levels were higher at all points in the curve.

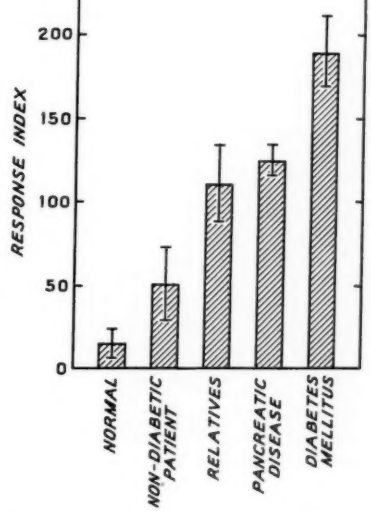

Fig. 4—Mean response indexes. Vertical bars represent standard errors.

The mean response indexes, which are the sum of the blood-sugar differences at each time-point as described above, are depicted in fig. 4. The response index was significantly greater in the relatives' group ($P < 0.01$) and in the pancreatic-disease group ($P < 0.005$) than in the normal group. It was also greater in the diabetics than in the normals ($P < 0.001$), in the non-diabetics ($P < 0.001$), and in the relatives ($P < 0.025$).

Discussion

To detect the prediabetic state Fajans and Conn (1954, 1959) applied the cortisone-augmented glucose-tolerance test. They gave 50 mg. of cortisone acetate (if the body-weight was over 160 lb., 62·5 mg.) by mouth eight and a half hours and two hours before the glucose. Their subjects so tested consisted of 104 controls, and 295 non-diabetic relatives of diabetics. They obtained an abnormal

curve or a positive response more frequently in non-diabetic relatives (25%) than in normal adults without a family history of diabetes (3%). They pointed out that the positive reactor to the cortisone glucose-tolerance test sometimes becomes diabetic within a relatively short period. This test procedure has been used by other workers (West 1957, German 1958, Goudie et al. 1958):

West (1957) applied the glucose-tolerance test, augmented with cortisone or prednisolone, in non-diabetic relatives of diabetics and in controls. He found that the relatives showed significantly higher two-hour values than the controls and that older people gave a positive response to this test more often than younger ones.

German (1958) performed the cortisone test of Fajans and Conn (1954) in 40 obese and 40 non-obese adults without evident family history of diabetes, and found no difference in response to the cortisone test between these two groups despite the well-known higher incidence of diabetes in the obese.

Goudie et al. (1958) applied the same cortisone test to 21 normal adults and 27 patients with symptomless glycosuria, 5 of whom had a family history of diabetes. In the standard glucose-tolerance test 9 of the 27 with glycosuria had a two-hour value of more than 120 mg. of blood-sugar (probable diabetes) and the other 18 had a lower two-hour value. The cortisone glucose-tolerance test did not reveal any significant differences in these two groups, and the investigation therefore regarded it as insufficiently sensitive for assessing the significance of glycosuria associated with a borderline glucose tolerance test.

Our results show that diabetics react to prednisolone more than do normal adults. Also prednisolone gave a high incidence of positive tests in non-diabetic relatives of diabetics (35%) and in people with a history of transient glycosuria of unknown origin.

The patients with chronic pancreatitis also showed an increased response to the prednisolone glucose tolerance test. Matsuda (1954), in our laboratory, performing *intravenous* glucose-tolerance tests in various pancreatic diseases, demonstrated impairment of glucose tolerance in 19 of the 21 patients with acute pancreatitis, in 7 of the 9 with chronic pancreatitis, and in all the 18 with pancreatic carcinoma. It is difficult, however, to demonstrate such impairment with the oral standard glucose-tolerance test. Most patients with pancreatic disease have too little islet-cell damage to produce an abnormal sugar-tolerance test. The present study suggests that the prednisolone glucose-tolerance test should be useful in the diagnosis of pancreatic disease.

The non-diabetic ill patients showed an apparently greater response than normal adults. Though the numbers are too small for statistical analysis, this finding is similar to that of Burn et al. (1953). Possible reasons for this difference between normal and ill subjects may include the reduced physical activity and the higher proportion of older people among the ill.

To draw a line dividing the corticosteroid glucose-tolerance curves into "normal" and "abnormal" is difficult because so many blood-sugar values are borderline. For the cortisone glucose-tolerance test Fajans and Conn (1954) regarded as positive a response in which the venous blood-sugar exceeded 160 mg. per 100 ml. at one hour and 140 mg. at two hours (Somogyi-Nelson method). (Their criteria for a normal standard glucose tolerance test included values of less than 160 mg. at one hour, 135 mg. at one and a half hours, and 110 mg. at two hours. Curves were interpreted as probable diabetes if the two-hour value was between 110 and 120 mg.) Our tentative criteria for a positive response to the prednisolone glucose-tolerance test, utilising capillary blood-sugar, are described above—namely, a peak level of more than 200 mg. per 100 ml. and a two-hour value of more than 140 mg. (Fujita-Iwatake method).

We regard the prednisolone glucose-tolerance test as useful in detecting slight impairment of carbohydrate metabolism and in reducing the number of borderline cases; but whether such a corticosteroid-primed test is more specific for diabetes mellitus is questionable.

For such a test prednisolone is perhaps preferable to cortisone because it has a stronger glucocorticoid action (Holten et al. 1957). The time of administration and the dosage of steroid hormone are also important. West (1959) found that the effect of prednisolone was greatest eight hours after oral administration.

Though the diabetogenic action of corticosteroids, in clinical dosage, is insufficient to cause a noticeable change in carbohydrate metabolism of the normal person, it is great enough to reveal a prediabetic state.

Summary

73 subjects were given the standard glucose-tolerance test and also a "prednisolone-sensitised" glucose-tolerance test. In the latter the procedure was the same except that 10 mg. of prednisolone was administered by mouth two hours before the ingestion of 50 g. of glucose.

All the diabetic patients and most of the patients with pancreatic disease reacted positively to the prednisolone-sensitised test. Also 6 of the 17 blood relatives of diabetics and 2 of the 3 subjects with a recent history of transient glycosuria but without a known family history of diabetes gave a positive response.

The average response index, which is the sum of blood-sugar differences between the standard curve and the prednisolone-sensitised curve at each time-point, and which represents the intensity of the reaction to prednisolone, was 15 for the normal subjects, 50 for the non-diabetic patients, 110 for the relatives of diabetics, 124 for the patients with pancreatic disease, and 189 for the diabetics.

The prednisolone glucose-tolerance test is useful in the detection of the prediabetic state and in the interpretation of borderline standard glucose-tolerance tests.

REFERENCES

Berger, H. (1952) *J. Amer. med. Ass.* **148**, 364.
Burn, T. W., Engle, F. L., Viau, A., Scott, J. L., Jr., Hollingsworth, D. R., Werk, E. (1953) *J. clin. Invest.* **32**, 781.
Downie, E. (1955) *Brit. med. J.* ii, 863.
Duncan, L. J. P. (1956) *Quart. J. exp. Physiol.* **41**, 453.
Fajans, S. S., Conn, J. W. (1954) *Diabetes*, **3**, 296.
— — (1959) *Ann. N.Y. Acad. Sci.* **82**, 208.
Fujita, A., Iwatake, D. (1931) *Biochem. Z.* **242**, 43.
German, J. L. (1958) *Diabetes*, **7**, 261.
Goto, Y., Seino, K., Ito, I. (1957) *Tohoku J. exp. Med.* **66**, 115.
— Ito, I., Seino, K. (1959) *ibid.* **69**, 113.
Goudie, R. B., Stamm, W. P., Dische, S. (1958) *J. Clin. Path.* **11**, 428.
Hagedorn, H. C., Jansen, B. N. (1923) *Biochem. Z.* **135**, 46.
Holten, C., Lundbaek, K., Staffeldt, I. (1957) *Acta med. scand.* **157**, 257.
Knight, W. A., Jr., Muether, R. O., Sommer, A. J. (1949) *Gastroenterology*, **12**, 34.
Matsuda, S. (1954) *Tohoku Igaku Z.* **49**, 693.
West, K. M. (1957) *Diabetes*, **6**, 168.
— (1959) *ibid.* **8**, 22.
Yamagata, S., Kanazawa, N., Orihara, S., Yanagawa, K., Sagisaka, R. (1956) *Rinsho-shokaki-byogaku*, **4**, 401.
Zucker, H. D. (1949) *Proc. Soc. exp. Biol., N.Y.* **71**, 597.

Addendum

To ascertain the difference between the blood-sugar values obtained by the non-specific sugar method and those obtained by the "true glucose" method, two blood-sugar determination methods were applied to the same blood specimen by one of us (Y. G.).

After administration of 50 g. of glucose by mouth, venous-blood specimens were obtained by antecubital venepuncture every hour for three hours, and the blood-sugar determinations

were made by the method of Hagedorn and Jensen and by the enzymatic glucose reagent method introduced by D. Keilin and E. F. Hartree (*Biochem. J.* 1948, **42**, 230). We used 'Glucostat' of Worthington Biochemical Corporation as a reagent.

The test was performed in 27 non-diabetic subjects. The Hagedorn-Jensen method gave higher blood-sugar values than the enzymatic method, the differences (mean ± standard error) being (mg. per 100 ml.):

Fasting	1 hour	2 hours	3 hours
24·5±1·7 mg.	25·1±2·4 mg.	26·4±2·5 mg.	24·6±1·7 mg.

TEST FOR ACTIVITY IN MAN OF PREPARATIONS CONTAINING GROWTH HORMONE

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IT is well known that growth hormone (somatotrophic hormone; S.T.H.) from human hypophysis is active in man, whereas S.T.H. from the hypophysis of other species has so far proved almost inactive. Since human S.T.H. is not obtainable in quantities sufficient for therapeutic purposes, we must hope that a natural source of active hormone may yet be found, or a chemical means of making inactive preparations active. Meanwhile the investigator needs a rapid and sensitive test of the activity, in man, of preparations under study.

I describe here a test which I have found useful though it is still empirical.

Method

The urine from young adult males is collected every 24 hours for up to 6 days. The preparation under test is injected on the morning of the 3rd day.

Every 24-hour urine sample is (a) acidified to pH 1 with concentrated hydrochloride acid and (b) extracted with chloroform. (c) The chloroform extracts are separated into benzene and water, and (d) the two fractions—the benzene-soluble and the water-soluble—of the chloroform extract of the urine are purified with Girard's reagent T. (e) The reducing power on phosphomolybdic acid is measured on each of the two purified fractions. (f) The reducing-power of the benzene-soluble fraction is expressed in milligramme-equivalents of deoxycortone (desoxycorticosterone) by comparing it with a curve prepared using known amounts of crystalline deoxycortone, and the reducing-power of the water-soluble fraction is expressed in milligramme-equivalents of cortisone by comparing it with a curve prepared using known amounts of crystalline cortisone. (g) On dividing the value of the benzene-soluble fraction by that of the water-soluble one, a quotient is obtained which I have called, in Italian "ste-ri quotient" (Patrono et al. 1954) (=quotient of the *r*educing *ste*roids).

From (b) to (d) inclusive, extraction is by the method of Talbot et al. (1945). (e) Method of Heard and Sobel (1946).

After administration of the preparation under test, an increase of my quotient greater than 100% of the average value of the two basic assays, or a quotient higher than 1, indicates that the preparation contains S.T.H. active in man.

Discussion

In 1951 Selye's idea of a dual pituitary regulation of the suprarenal secretion sounded interesting: just as A.C.T.H. stimulated the secretion of glucocorticoids, so S.T.H. stimulated the secretion of mineralocorticoids. At that time some workers, including myself, believed that separation into benzene and water of the ketonic reducing material which could be extracted with chloroform from urine would allow separate assay of (1) poorly water-soluble substances similar to the deoxycorticoids (among which there are metabolites of the mineralocorticoids), and (2) readily water-soluble substances similar to the 11-oxycorticoids (among which are metabolites of the glucocorticoids). Accordingly, in 1951, I suggested to my collaborators Natoli and Zilli that, using the above method, they should assay the urinary reducing steroids in a group of patients with Cushing's syndrome and in a group of patients with acromegaly. These researches showed that in Cushing's syndrome there was an increase of both the poorly water-soluble and the readily water-soluble fractions of the ketonic steroids which reduce phosphomolybdic acid. In the urine of the acromegalic patients, on the other hand, only the poorly water-soluble fraction was increased (Natoli and Zilli, 1952).

These results led me to start a large number of investigations, using the above method, even though it was open to criticism and no longer much used for assaying urinary "corticoids". The most important results of my research on the ste-ri quotient are:

(1) Urinary assays performed on 320 normal subjects of both

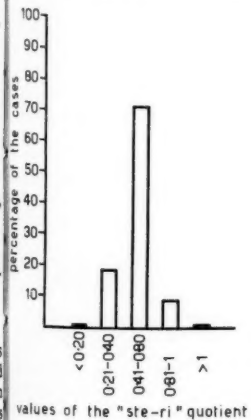

Fig. 1.

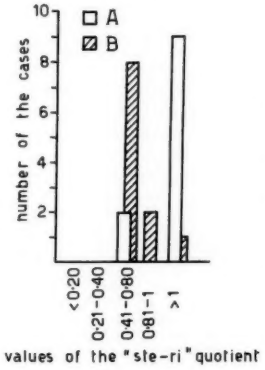

Fig. 2.

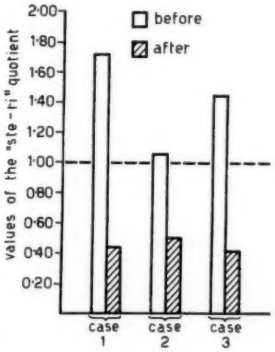

Fig. 3.

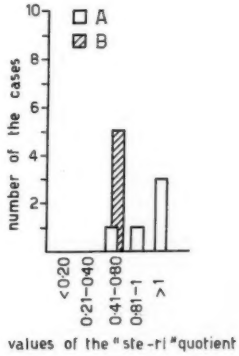

Fig. 4.

Fig. 1—Percentage distribution of the values of the ste-ri quotient in 320 normal subjects.

Fig. 2—Values of the ste-ri quotient. (A) 11 cases of "active" acromegaly. (B) 11 cases of "inactive" acromegaly.

Fig. 3—Values of the ste-ri quotient in 3 cases of "active" acromegaly before and after roentgentherapy on the hypophysis.

Fig. 4—Values of the ste-ri quotient; A: large newborn; B: normal newborn.

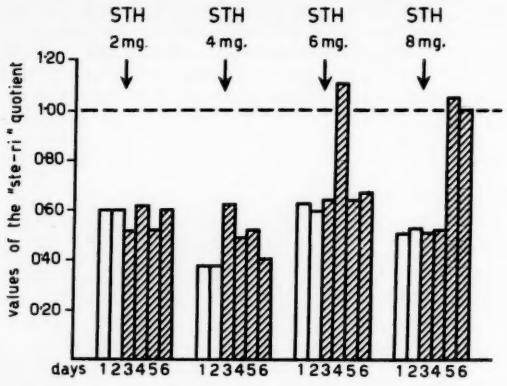

Fig. 5—Modifications of the ste-ri quotient in 4 young men treated only once with four different doses of S.T.H. extracted from human hypophysis according to the method of Li and Papkoff.

sexes, aged from 5 to 80 years, have shown that in over 99%, not treated with hormones, my quotient is lower than 1·0. (For example: poorly water-soluble fraction=0·55 mg. per 24 hours; readily water-soluble fraction=1·10 mg.; ste-ri quotient =0·50). The percentage distribution of the values is shown in fig. 1 (Patrono 1959).

(2) Only in acromegalic patients, during an active phase of their disease have we often found a ste-ri quotient higher than 1·0. (For example: poorly water-soluble fraction=1·37 mg. per 24 hours; readily water-soluble fraction=0·88 mg.; ste-ri quotient=1·55). Fig. 2 shows the quotient value obtained (A) in 11 cases of "active" acromegaly, and (B) in 11 cases of "inactive" where the disease was either spontaneous or because of therapy (Patrono et al. 1957).

(3) In 3 cases of "active" acromegaly, after irradiation of the hypophysis, my quotient rapidly fell to less than 1·0 (fig. 3). (For instance: before treatment, poorly water-soluble fraction =1·59 mg. per 24 hours; readily water-soluble fraction =0·92 mg.; ste-ri quotient=1·73. After treatment, poorly water-soluble fraction=0.37 mg.; readily water-soluble fraction=0·85 mg.; ste-ri quotient=0·43) (Patrono et al. 1957).

(4) A quotient above 1·0 is also found quite frequently in large newborn infants (de Pedrini 1958). Fig. 4 compares such infants with the normal.

(5) Of all the hormones which can be extracted from the hypophysis only S.T.H. has raised my quotient above 1·0. (Corticotrophin 200 mg., in 2 days, lowers it by 20–50%, by causing a relative increase of the readily water-soluble fraction.) Such a rise is seen after a single injection of 6–8 mg. of S.T.H. extracted from human hypophysis (Patrono and Nicolosi 1959, Nicolosi et al. 1959) (fig. 5), whereas it was seen in only 2 out of 9 subjects given an injection of S.T.H. extracted from beef hypophysis in a dosage of 1 mg. per kg. body-weight (average 65 mg.) (de Pedrini et al. 1953).

Now my collaborators and I are trying to single out the urinary steroids which "run" under the action of S.T.H. This, we hope, will give a more scientific basis to my test, which at present remains empirical.

Summary

A single injection of a small amount of growth hormone (somatotrophic hormone) obtained from human pituitary gland raises, in man, a quotient obtained by dividing the value of the benzene-soluble fraction by the value of the water-soluble fraction of the urinary ketone steroids which reduce phosphomolybdic acid. This empirical test should be useful for the detection, in material of animal origin, of growth hormone which is active in human beings.

References at foot of next column

RUPTURED ABDOMINAL AORTIC ANEURYSMS

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ALTHOUGH resections of ruptured abdominal aortic aneurysms, with graft replacement, are reported with increasing frequency (Cooley and DeBakey 1954, Cooley 1955, Javid et al. 1955, Schumaker and King 1955, Elliott et al. 1959, Mavor et al. 1959) the case-mortality remains high and many problems in management are unsolved. Mavor et al. (1959) have recently discussed these problems in relation to four surgically treated cases of which one survived for 18 months, and Elliott et al. (1959) have described a series of twenty-four cases with nine survivals of over a month. Experience of such cases is not easily acquired, however, and this is why we report the following five patients treated by resection. In the 3-year period during which they were seen at the hospitals of the South Warwickshire group a further five cases were admitted, but for various reasons they were not treated surgically. With increasing knowledge some of them might well have been saved.

Case-reports

THE UNTREATED CASES

Case 1.—A man, aged 79, was admitted to hospital on Aug. 11, 1956, having collapsed 2 hours previously after a meal. His health had been good except for symptoms of prostatism. He was severely shocked and his blood-pressure was unrecordable. There was generalised abdominal tenderness and guarding especially on the right. He was treated for shock and hæmorrhage and his blood-pressure improved temporarily to 110/60 mm. Hg. He then collapsed again and he died 4 hours after admission. Necropsy confirmed the presence of a ruptured abdominal aortic aneurysm.

Case 2.—A 67-year-old man was admitted to a medical ward on Nov. 12, 1957, for stabilisation of diabetes mellitus. 12 days later he suddenly vomited 6 oz. of stale blood. He was pale and sweating, but his pulse and blood-pressure were satisfactory. He vomited blood three more times, and 5 hours after the onset of hæmatemesis he collapsed and died. Postmortem revealed an aneurysm of the aorta below the renal arteries; a $1^1/_2$-in. tear in the posterior wall led into a false aneurysmal sac lying behind and to the left of the aorta. The fourth part of the duodenum formed part of the superior border of the sac, and the aneurysm had ruptured into the general peritoneal cavity and into the duodenum. The general peritoneal cavity and the stomach and intestines were filled with recent blood-clot.

Case 3.—A man, aged 71, was found collapsed about 2 hours before admission to hospital on Jan. 30, 1958. Apart from increasing dyspnœa during the previous 3 months he had been fit. He was pale, cold, and dyspnœic; the blood-pressure was 40/0. A tender abdominal mass present on the right was not pulsatile. A noradrenaline infusion was started until blood

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de Pedrini, P. (1958) *Gazz. int. Med. Chir.* **63,** 3377.
— di Girolamo, L., Magliocca, R., Natoli, A., Patrono, V. (1953) *Endocr. Sci. Cost.* **21,** 289.
Heard, R. D. H., Sobel, H. (1946) *J. biol. Chem.* **165,** 687.
Natoli, A., Zilli, E. (1952) *Settim. med.* **40,** 41.
Nicolosi, G., Cavina, G., Cordova, C., Patrono, V. (1959) *Folia endocrin. Pisa,* **12,** 771.
Patrono, V. (1959) *Progr. med., Napoli,* **15,** 293.
— de Pedrini, P., di Girolamo, L. (1954) *Folia endocrin., Pisa,* **7,** 321.
— — — (1957) *Rif. med.* **71,** 1429.
— Nicolosi, G. (1959) *Progr. med., Napoli,* **15,** 428.
Talbot, N. B., Saltzmann, A. H., Wixom, R. L., Wolfe, J. K. (1945) *J. biol. Chem.* **160,** 535.

for transfusion became available, but he did not respond and he died 2 hours later. Necropsy revealed the rupture of a large aortic aneurysm on the right.

Case 4.—A woman of 87, admitted to hospital on April 9, 1958, had a 24-hour history of acute upper abdominal pain, copious vomiting, and constipation. Her previous health had been good apart from anæmia and mild vascular insufficiency in her legs. She was severely shocked; the blood-pressure was 80/40. Her abdomen was distended and tender, with a large midline pulsating swelling felt in the epigastrium. A ruptured aortic aneurysm was diagnosed, and resuscitation was begun. Temporary improvement followed blood-transfusion, but she collapsed again and died 14 hours after admission. The diagnosis was confirmed post mortem.

Case 5.—A man of 76, admitted to hospital on May 4, 1959, had had a fainting attack 12 hours previously accompanied by pain in the lower right quadrant of the abdomen and nausea. For 5 months he had been treated in the orthopædic department for pain in the right thigh and leg. He was pale, cold, and clammy; his blood-pressure was 100/70. There was rigidity and tenderness in the right iliac fossa, but no mass or abnormal pulsation was felt. A ruptured abdominal aneurysm was diagnosed. His condition failed to improve, and his blood-pressure fell progressively despite transfusion of 9 pints of blood. It was decided nevertheless to operate, but he died suddenly while final preparations were being made 8 hours after admission. Necropsy showed a ruptured aortic aneurysm, with old and recent clot in the retroperitoneal tissues.

THE SURGICALLY TREATED CASES

Case 6.—A man, aged 70, was admitted to hospital on April 2, 1958, with sudden severe upper abdominal pain radiating through to the back, of 2 hours' duration. He had vomited twice and his bowels had acted normally earlier the same day. He had had previous mild attacks of pain in the same region for the past year, and 3 years previously an abdominal aortic aneurysm had been diagnosed at another hospital, but he had not had surgical treatment.

The patient was severely shocked—pale, anxious, restless, and thirsty—and in great pain. His blood-pressure was 100/70 and pulse-rate 130 per min. The upper abdomen was tender, with guarding, and a large pulsating swelling was felt in the epigastrium and umbilical region. A ruptured aortic aneurysm was diagnosed.

After treatment of the shock by blood replacement, operation was performed 2 hours after admission. The aneurysm was explored by a thoracoabdominal approach. The lower thoracic aorta was dissected free for about 5 cm., and an occlusive clamp was placed ready for use in the event of sudden hæmorrhage. The aneurysm, which had ruptured, extended from 1 cm. below the renal arteries down to and including the aortic bifurcation. The aneurysmal sac was excised and replaced by an 'Orlon' bifurcation graft.

The postoperative period was satisfactory except for an area of infected collapse in the upper lobe of the left lung which cavitated, but resolved with antibiotic therapy. On the 2nd postoperative day there was oliguria and the blood-urea rose to 70 mg. per 100 ml., but thereafter renal function returned rapidly to normal. When last seen, 18 months later, he was very well.

Case 7.—A man of 71 was admitted on Aug. 26, 1958, with a history of right-sided abdominal pain radiating through to the back for 4 days. 3 hours previously it had become very severe. There had been no nausea or vomiting. An abdominal aneurysm had been diagnosed a year earlier but in view of associated disease, which included a duodenal ulcer, gallstones, diverticulitis, and prostatic hypertrophy, elective surgery had not been advised.

The patient was pale, sweating, and dyspnœic. His blood-pressure was 130/80, and pulse-rate 100. His abdomen was distended. A mass, about 4 in. in diameter in his left iliac fossa, was pulsatile and tender. A ruptured aneurysm of the abdominal aorta was diagnosed.

After resuscitation with 7 pints of blood operation was performed by a thoracoabdominal route. An open clamp was placed in position across the lower thoracic aorta. The ruptured aneurysm extended from just below the renal vessels and involved the common iliac arteries. The aneurysmal sac was excised and replaced by an orlon bifurcation graft. Because of unrecognised faulty technique in preparation of the graft, however, blood-loss from the seams after removal of the occlusive clamp was profuse. The hæmorrhage was controlled by reapplication of the clamp, but despite rapid blood replacement, the patient died shortly afterwards.

Case 8.—A man, aged 76, was admitted to hospital on Dec. 16, 1958. For the previous 24 hours he had had abdominal and low-back pain, and he had vomited once. He had had no earlier symptoms apart from nocturnal frequency of micturition. He was pale and sweating profusely. His blood-pressure was 100/60, and his pulse rapid and irregular. There was a large tender pulsating abdominal mass in the midline. A ruptured abdominal aortic aneurysm was diagnosed.

At operation, performed 4 hours later after blood-transfusion, the diagnosis was confirmed. The approach was thoracoabdominal, and the lower thoracic aorta was secured prophylactically with an unclosed occlusive clamp. The aneurysm was confined to the aorta below the renal vessels, and after excision it was replaced by an orlon graft. After operation the patient developed severe oliguria, and next day his blood-urea was 119 mg. per 100 ml. His condition continued to deteriorate, and he died on the 3rd day after operation.

Case 9.—A woman of 70 was admitted to hospital on Jan. 13, 1959, with a 10-hour history of lower abdominal pain which radiated through to the back. She had vomited four times. During the previous 2 years she had been aware of "throbbing" in the lower abdomen. She was pale and sweating, her blood-pressure was 120/80, and her pulse-rate 64. There was generalised tenderness and guarding of the abdomen, and a large pulsatile abdominal mass was palpable. A ruptured abdominal aortic aneurysm was diagnosed, and this was confirmed at operation 6 hours after admission.

The aneurysm was explored through a long left paramedian incision. Because it appeared to involve the renal vessels the aneurysm was considered unresectable, and the abdomen was closed. Except for oliguria for the first 2 days after operation the patient made a satisfactory recovery.

A second operation was performed 8 days later, after a retrograde femoral aortogram. A thoracoabdominal approach was used. The lower thoracic aorta was dissected free and an occlusive clamp was placed in position ready for control if necessary. The aneurysm was resected, leaving its posterior wall in situ, and replaced by an orlon graft. In the postoperative period the patient again developed oliguria, and the blood-urea rose to 73 mg. per 100 ml. a week after operation. Her renal function recovered quickly, however, and she had an uneventful convalescence. A year after operation she remains well.

Case 10.—A man, aged 64, was admitted to an orthopædic ward on Aug. 24, 1959. He had had outpatient treatment for pain in his left hip and thigh which was thought to be due to an L3-root syndrome. An exploratory laminectomy was performed next day, but no abnormality was found. His postoperative progress was uneventful, apart from continued pain in the left hip, until 10 days later when the pain spread into the left side of the abdomen. He was pale; the pulse-rate was 100 per min., and the blood-pressure 160/100. A large hard mass, tender and pulsatile, was palpable on the left side of the abdomen. Next day the abdominal mass increased considerably in size and the patient's general condition deteriorated. A ruptured abdominal aneurysm was diagnosed and operation was performed on Sept. 7 after resuscitation by blood-transfusion.

The abdomen was opened through a long left paramedian incision, and an aneurysm was found, limited to the aorta below the renal vessels. The aneurysmal sac was excised and replaced by a 'Teflon' bifurcation graft. In the immediate postoperative period oliguria was serious, and by the 4th day

the blood-urea had risen to 134 mg. per 100 ml. But the urinary output gradually improved, and by the 14th post-operative day the blood-urea had returned to normal.

The patient was discharged from hospital 6 weeks after operation. 4 weeks later he was readmitted with severe melæna. He was pale and sweating, and a large mass was felt on the left side of his abdomen. After resuscitation operation was performed (Nov. 18). He was found to have a massive retro-peritoneal hæmatoma which had perforated into the pelvic colon, and he died during the operation. At postmortem all suture lines of the graft were intact, but the anterior surfaces of the lumbar vertebræ were much eroded, and this appeared to be the source of the massive hæmorrhage.

Discussion

We shall here consider only those aspects of the management of ruptured aortic aneurysm which have been particularly impressed on us by our series. The patients in both groups were old, and most of them had associated degenerative diseases which made them poor anæsthetic and surgical risks. Some cases were admitted to medical wards, and physicians should be increasingly on the watch for the condition if delays in treatment are to be avoided. Diagnosis proved difficult in only three patients (cases 1, 2, and 3), and it was made before operation in all those treated surgically. Gastrointestinal hæmorrhage, as in case 2, is an unusual method of presentation, but even so there may still be time for surgical intervention (Voyles and Moretz 1958). In one case only during this 3-year period has the diagnosis of an acute rupture been proved incorrect at operation, and that was in a woman of 65 with a known aneurysm who was awaiting resection. Sudden severe abdominal pain developed, radiating through to the back, and accompanied by shock. Exploration showed no extravasation of blood, but the walls of the aneurysm were congested, red, and œdematous. She probably belonged to the group of "acute aneurysms" referred to by Elliott et al. (1959). The ætiology is uncertain but the symptoms probably result from partial tears of the aneurysmal wall, which may be a prelude to complete rupture. Certainly severe attacks of back pain often precede rupture, and these were present in four patients (cases 6, 7, 8, and 9). It is less generally realised that pain may be referred, before rupture, entirely to the buttock and leg, making differential diagnosis from other forms of root pain difficult. This was seen in cases 5 and 10.

In both our groups an interval of at least a few hours, and sometimes longer, elapsed between the rupture of the aneurysm and the severe collapse which often precedes death. In some cases shock was not very evident in the early stages, and the blood-pressure was well maintained during this time. In our experience, once deterioration has started, it is usually progressive, and it may continue despite attempts to treat the hæmorrhage and shock by blood-transfusion and sedation. This is probably due to the gradually increasing retroperitoneal hæmatoma acting reflexly through the autonomic nervous system, as the actual blood-loss is often slight and does not seem commensurate with the degree of shock. For this reason we urge early operation, while resuscitation is in progress, instead of waiting hopefully for improvement—a policy which may have cost the lives of cases 1, 4, and 5. Evacuation of the hæmatoma and control of the source of bleeding appear necessary to reverse the shock and hypotension, which are also important factors in the causation of later deaths from renal failure.

Anæsthesia in patients with ruptured aortic aneurysms presents special problems, especially if a transthoracic extension is made to the abdominal incision. We would emphasise that the general standards of fitness for operation may have to be relaxed if lives are to be saved. Hypothermia was used in only one case in our series, and it was not continued once the aneurysm was seen to be below the renal arteries (case 10). Fortunately this is so in the majority of cases. Where the aneurysm extends above the renal arteries it is probably safer to divide the widened aorta below them, using the wide cuff for anastomosis to the graft, provided of course that the rupture is below this point.

Much discussion has centred round the need for ensuring access to the lower thoracic aorta for rapid and efficient control of bleeding should this arise (Gerbode 1954, Javid et al. 1955, Mavor et al. 1959, Savage 1959). This was done in four of our five surgically treated cases, and it proved of great value in two (cases 6 and 8) but was probably unnecessary in the others. It is not easy to decide beforehand in which cases it will be necessary, but where proximal extension of the retroperitoneal hæmatoma makes access to the upper abdominal aorta difficult, the manœuvre is valuable despite the hazards that it must add to the operation. The upward extension of the hæmatoma has another important aspect—namely, that it may make the aneurysm appear to the inexperienced to extend above the renal vessels, making the condition seem unsuitable for surgery. This happened in case 9, the patient surviving the laparotomy and the immediate effects of the rupture and undergoing successful resection a week later.

One of the most serious complications of the surgical treatment of abdominal aneurysms is renal failure. Various factors are responsible, including hypotension before, during, and after operation. In addition the renal arteries may be obstructed directly or from spasm, embolism, or intimal rupture during the application of the occlusive clamp, because so short a segment of aorta usually remains after division above the aneurysm. One death (case 8) was due to uræmia, and two of the other three patients who survived operation had temporary renal impairment as shown by oliguria and a raised blood-urea for the first few days. We feel that, whenever oliguria threatens, no time should be lost in determining its cause and instituting treatment by standard methods. Any delay may result in irreversible renal damage. One late death (case 10) 9 weeks after operation was due to sudden massive hæmorrhage from the region of the graft. All suture lines were intact at operation and at necropsy, and the graft was not redundant in length. Gross erosion of the anterior surfaces of the vertebral bodies lying behind the graft was thought to be the cause of the bleeding.

Conclusion

Ten cases of acutely ruptured abdominal aortic aneurysm admitted during the past 3 years have been reviewed. Awareness of unusual methods of presentation, with earlier operation, massive blood replacement, courageous anæsthesia, and increasing surgical experience should do much to reduce the present high case-mortality of the condition.

REFERENCES

Cooley, D. A., DeBakey, M. E. (1954) *Postgrad. Med.* **16**, 344.
— (1955) *Ann. Surg.* **142**, 621.
Elliott, J. A., McKenzie, A. D., Chung, W. B. (1959) *Surgery*, **46**, 605.
Gerbode, F. (1954) *Surg. Gynec. Obstet.* **98**, 759.
Javid, H., Dye, W. S., Grove, W. J., Julian, O. C. (1955) *Ann. Surg.* **142**, 613.
Mavor, G. E., Davidson, L. D., Clark, C. G. (1959) *Brit. J. Surg.* **47**, 262.
Schumaker, H. B., King, H. (1955) *A.M.A. Arch. Surg.* **71**, 768.
Savage, C. R. (1959) *Brit. J. Surg.* **47**, 257.
Voyles, W. R., Moretz, W. H. (1958) *Surgery*, **43**, 666.

A CASE OF MALIGNANT TERTIAN (PLASMODIUM FALCIPARUM) MALARIA AFTER BLOOD-TRANSFUSION

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THE accidental transmission of malaria by transfusion of fresh blood has been recognised since 1911 (Woolsey). In 1936 Thomas et al. described the first case in Britain.

Hutton and Shute (1939) pointed out that storage of blood at low temperatures (4–6°C—i.e., 39–42°F) for days or even weeks fails to destroy the malarial parasite. Malaria following the transfusion of stored blood was reported for the first time by Gordon (1941). This was due to *Plasmodium malariæ*.

In these cases of accidentally transmitted malaria, all the donors had of course been resident for a time in malarious areas. Some had afterwards lived outside such areas for over 20 years without having symptoms (McClure and Lam 1945, Wright 1938).

Although parasites were demonstrated in some donors who gave no history of malaria, more often no parasites were found (Wright 1938). Even special techniques failed to recover parasites from the donor (Sharnoff et al. 1945).

Most reported cases have been due to *P. malariæ* and *P. vivax*. Few cases of *P. falciparum* malaria after blood-transfusion have been recorded (Gubb 1919, Das Gupta 1943, Chen and Wu 1946, Coda et al. 1954). Hence the following case of *P. falciparum* malaria after blood-transfusion seems worth reporting, particularly as increasing numbers of blood-donors have lived in areas where malaria is endemic. We believe it to be the first case of *P. falciparum* malaria following blood-transfusion to be described in this country.

Case-report

A woman, aged 41, was admitted to hospital in August, 1959, with anæmia, ankle œdema, and steatorrhœa. She was born in England and had never been abroad.

On Aug. 20 she was transfused with two pints of stored blood, one of which was from a Nigerian donor. Laparotomy was performed next day, and a segment of thickened jejunum was resected. She received a third pint of stored blood during operation.

Her recovery was uneventful until the evening of the 16th postoperative day, when she had a mild rigor with a temperature of 101°F. On the 17th, 18th, 20th, and 21st days she had an evening pyrexia (101–103°F) without rigor but accompanied by a feeling of coldness followed by hotness. On the 22nd postoperative evening she had a second rigor (temperature 105°F). 2 days later her spleen was easily palpable, and that evening she had a further rigor.

Large numbers of ring forms of plasmodium were found in a thin blood-film taken during the rigor. Two gametocytes (crescents) of *P. falciparum* were found in a thick blood-film taken 24 hours later, whereas careful examination of several thin and thick blood-films taken before this showed only ring forms.

The patient was treated with chloroquine phosphate 600 mg. (base), followed in 6 hours by 300 mg., and then by 300 mg. daily for 2 days (Colonial Medical Research Committee 1954). She made a complete recovery. She has had no further symptoms of malaria, and no parasites have been found in subsequent blood-films.

Investigation of Donors

The patient had been transfused with three pints of stored blood drawn from different donors. Two of the donors had lived in England all their lives, and were therefore not investigated. The third donor was a 19-year-old male Nigerian, who had arrived in England from Lagos in June, 1959. His blood was drawn on Aug. 6 and stored for 14 days at a temperature of 4–6°C (39–42°F) before use. Although he denied any history of malaria, he seemed to be the most likely source of infection because he was the only donor who had recently lived in a malarious area. Yet examination of a number of thick and thin films of his blood by two microscopists for 3 hours failed to reveal any parasites.

Despite this negative finding we decided to continue the search for parasites, and a further series of blood-films was made 10 days later. After a long search, one female gametocyte (crescent) of *P. falciparum* was found in a thick film, and later two merozoites of the same species were also found. This confirmed that the Nigerian was the infective donor. During examination of further blood-films we were surprised to observe a number of parasites of a second species of plasmodium, *P. malariæ*.

We also decided to take this opportunity of confirming the action of the drug chloroquine phosphate, a single 600 mg. (base) dose of which is said to render the peripheral blood of malaria-carriers free of parasites within a few hours (World Health Organisation 1955). On Dec. 16 10 ml. of venous blood from the Nigerian donor was injected intramuscularly into a volunteer. Immediately after the blood had been drawn the donor was given 600 mg. (base) chloroquine phosphate. $3^1/_2$ hours later a further 10 ml. of blood was taken and injected into a second volunteer. *P. falciparum* asexual parasites were found in thick blood-films taken from the first volunteer after 9 days. No parasites have been found in the blood of the second volunteer, despite daily examination of thick blood-films.

Examination of blood-films and the injection of blood from the Nigerian donor into a volunteer showed beyond doubt that this donor's blood was the source of infection in our patient. The lengthy and laborious examinations necessary to find parasites in the blood-films illustrate the need for careful, painstaking, and repeated laboratory investigation of donors in cases of suspected accidental transmission of malaria.

Discussion

The possibility of malarial transmission has long been recognised by the National Blood Transfusion Service. All donors are specifically questioned before blood is taken. A positive history does not necessarily debar the donor, but the blood is used for plasma (or serum) extraction, and the potentially dangerous cells are not transfused. The extreme rarity of reported cases of transmitted malaria reflects the success of this policy.

Conditions affecting the risk of malarial transmission are changing, however. Greatly increased air travel may allow entry into the country of people incubating the disease after even the shortest stay in malarious areas. In at least one case infection occurred during a 1-hour " stop-over " of a plane flight between two non-malarious areas. Secondly, immigrants from endemic malarious areas have settled in this country in recent years. Many may deny having had clinical malaria, but having acquired immunity through infection in childhood they may be carriers. This is certainly true of our Nigerian donor.

If such blood has to be used for transfusion a single dose of chloroquine 600 mg. (base) should be given a few hours before taking blood. Provided reinfection does not occur, chloroquine nearly always sterilises *P. falciparum* infections; but exoerythrocytic parasites (liver stage) may be present in both *P. vivax* of *P. malariæ* infections, and cause relapses. Irrespective of the age of the original malaria infection with *P. vivax* or *P. malariæ* parasites, the dose of chloroquine should be repeated each time such a subject acts as a donor.

In the absence of clinical or laboratory criteria, the present policy of the National Blood Transfusion Service of considering all such volunteers as potential carriers, irrespective of history, is the only safe one. With these precautions transmission of malaria by blood-transfusion will be rare. But in a fever of uncertain origin following transfusion, malaria should be considered as a possible cause.

Summary

For the first time in this country, *Plasmodium falciparum* malaria following blood-transfusion is reported. In a non-immune person this is a potentially fatal disease.

The patient had several individual attacks of fever unaccompanied by rigor. This is the usual picture in primary *P. falciparum* malaria.

The infected blood had been stored for 14 days at 4–6°C (39–42°F) before use. There is evidence that this is by no means the limit of viability of the parasite.

All donors who have stayed in malarious areas for even short periods are potential carriers, and their blood should be used only for plasma (or serum) extraction.

Chloroquine renders the peripheral blood of chronic carriers free of asexual parasites within a few hours.

In a fever of unknown origin following blood-transfusion the possibility of malaria should be considered.

We wish to express our thanks to Dr W. E. Mahon, physician, Woolwich Group of Hospitals, for permission to publish this case; to Mr. C. Tidd, former senior bacteriological technician, Brook General Hospital, for finding the gametocytes of *Plasmodium falciparum* in the patient's blood; and to Miss M. Maryon, chief laboratory technician, Malaria Reference Laboratory, for her untiring efforts in helping to find the parasites in blood-films from the Nigerian donor and first volunteer, and for help with references.

REFERENCES

Chen, J. H., Wu, Y. K. (1946) *Chin. med. J.* **64,** 309.
Coda, D., Pontes, J. F., Coda, M. De M. (1954) *Folia clin. biol., S. Paulo,* **32,** 105.
Colonial Medical Research Committee (1954) Recommendations on the Use of Antimalarial Drugs. London.
Das Gupta, C. R. (1943) *Indian med. Gaz.* **78,** 384.
Gordon, E. F. (1941) *J. Amer. med. Ass.* **116,** 1200.
Gubb, A. S. (1919) *Brit. med. J.* ii, 74.
Hutton, E. L., Shute, P. G. (1939) *J. trop. Med. (Hyg.),* **42,** 309.
McClure, R. D., Lam, C. R. (1945) *Surg. Gynec. Obstet.* **80,** 261.
Sharnoff, J. G., Geiger, J., Selzer, I. (1945) *Amer. J. clin. Path.* **15,** 494.
Thomas, W. L., Keyes, S., Dyke, S. C. (1936) *Lancet,* i, 536.
World Health Organisation (1955) Chemotherapy of Malaria. Monograph series no. 27.
Woolsey, G. (1911) *Ann. Surg.* **53,** 132.
Wright, F. H. (1938) *J. Pediat.* **12,** 327.

Preliminary Communication

ASEPTIC MENINGITIS ASSOCIATED WITH A PREVIOUSLY UNRECOGNISED VIRUS

DURING 1959 a virus which could not be identified as any recognised type was isolated from the fæces of 61 patients admitted to hospital with aseptic meningitis. A further 8 patients with aseptic meningitis showed serological evidence of infection with the same virus though it was not isolated from their stools, making a total of 69 cases apparently due to the same agent. At present the virus is referred to as Frater virus after the type strain.

The cases occurred in an outbreak which reached its peak in August and September, 1959, and were distributed widely over the whole of Central Scotland with over half in the cities of Glasgow and Dundee. Almost 60% of the patients were children of school age, a considerable number were adults, and the full range of ages was from 4 months to 39 years.

INVESTIGATIONS

The virological investigation of these patients consisted in the examination of stools for virus, and of sera taken at the acute and convalescent stages of illness for antibodies. Technical methods are described elsewhere.[1] Stool extracts were tested in human-thyroid, human-amnion, and monkey-kidney tissue cultures, and virus isolates were identified as Frater virus by neutralisation tests with an antiserum made by immunising a guineapig with the type strain of Frater virus.

1. Duncan, I. B. R. *Arch. Virusforsch.* (in the press).

Stool specimens were received from 68 of the 69 patients in the series and Frater virus was isolated from 61. Paired acute-phase and convalescent-phase sera were obtained from 46 of the 69 patients. There was a 4-fold or greater rise in titre of Frater antibodies between the two specimens in 26; in 14 other pairs titres (expressed as reciprocals of final serum dilutions) of 64 or more were found in both sera but without a 4-fold rise; and in 6 pairs titres of 16 or less were found in both. A single convalescent-phase serum only was obtained from 10 further patients in the series. 8 had titres ranging from 64 to 4096 and 2 had titres of 32 or less.

The interpretation of raised titres in single convalescent sera, and in pairs with the same level in both, is possible only if the level of antibodies to the virus in the general population is known. To determine this, 117 sera taken from blood-donors six months before the outbreak of aseptic meningitis were titrated for antibodies to Frater virus. The levels were: under 8, 91%; 8, 7%; 16, 2%. These results strongly suggest that a titre of 64 or more may be taken as evidence of recent infection with Frater virus. Thus sera from 56 of the 69 patients in the series were tested, and definite evidence obtained in 26 cases and suggestive evidence in 22 that infection with Frater virus coincided with the clinical manifestations of aseptic meningitis.

Further evidence of the connection between Frater virus and aseptic meningitis is afforded by the much greater frequency of isolation of the virus from the stools of patients with aseptic meningitis than of control patients. During the six months from July to December, 1959, stool specimens from 165 patients with aseptic meningitis were examined and Frater virus isolated from 61, an isolation-rate of 37%. During the

ISOLATIONS OF FRATER VIRUS FROM STOOLS OF ASEPTIC MENINGITIS CASES AND CONTROL PATIENTS, JULY-DECEMBER, 1959

Age (years)		0–4	5–9	10–19	20+	All ages
Aseptic meningitis	Total number of patients	41	45	46	33	165
	Number from whom virus isolated	9 (22%)	19 (42%)	22 (48%)	11 (33%)	61 (37%)
Control group	Total number of patients	94	27	42	52	215
	Number from whom virus isolated	6 (6%)	2 (7%)	4 (9%)	0 (0%)	12 (6%)

same period Frater virus was isolated from only 12 of 215 patients without symptoms of aseptic meningitis, an isolation-rate of 6%. These control patients were admitted to hospital with non-infectious neurological diseases, diarrhœa, and respiratory diseases. The table shows that the greater frequency of isolation of Frater virus from aseptic meningitis patients held true at all age-groups. These findings appear to fulfil the requirements of the Committee on the Enteroviruses [2] for the establishment of an ætiological connection between an enterovirus and a particular disease.

In addition to the 69 cases of aseptic meningitis, 1 case [3] of paralytic disease clinically indistinguishable from poliomyelitis was found to be associated with Frater virus. Poliovirus was not isolated from this patient—a baby of 1 year—and there was no clear serological evidence of recent poliomyelitis infection.

THE VIRUS

Frater virus is not yet fully identified. The characters of the virus so far determined suggest that it belongs to the enterovirus group.

It is cytopathogenic—with changes like those of enteroviruses—in tissue cultures of human thyroid, human amnion, and rhesus-monkey kidney, and is not cytopathogenic in HeLa cells. From 10- to 100-fold higher titres in thyroid than in amnion, and in amnion than in kidney, are found when the same seed is titrated in all three tissues. When 75 stool extracts known to contain Frater virus were tested in parallel in the three tissues, 65 isolations were made in thyroid, 58 in amnion, and 26 in kidney. The virus is non-pathogenic for suckling mice, adult mice, and guineapigs, and for chick embryos by various routes of inoculation.

In this laboratory the virus was not neutralised by antisera, made by immunising rabbits, to polioviruses types 1, 2 and 3, Coxsackie viruses types A7 and 9 and B1 to 5, and ECHO viruses types 1 to 9, 11 to 15, and 17 to 20. Antisera to Frater virus, made by immunising guineapigs, failed to neutralise prototype strains of polioviruses types 1, 2 and 3, Coxsackie viruses types A7 and 9 and B1 to 6, and ECHO viruses types 1 to 27. Dr. A. D. Macrae of the Central Public Health Laboratory, Colindale, also examined the virus and reported that it was not neutralised by his antisera to Coxsackie A9 or B1 to 5, or ECHO 1 to 27. It has now been sent to Dr. J. Melnick for further examination. Complement-fixation tests of the virus were negative with adenovirus and herpes simplex antisera and positive with sera known to contain neutralising antibodies to Frater virus. Pooled human gamma-globulin neutralised the virus to a titre of 32. It is a relatively stable virus and is ether-resistant.

Frater virus has the properties of an ECHO virus as laid down by the Committee on the ECHO Viruses.[4] Serologically it differs from ECHO types 1 to 27, and its growth in tissue culture is very different from that of 2060 virus of Mogabgab and Pelon [5] which is now designated as ECHO type 28.[6] Frater virus appears, therefore, to be a new ECHO virus or an antigenic variant of an existing one.

SUMMARY

In 1959 69 cases of aseptic meningitis in Central Scotland were found to be associated with a previously unrecognised virus, apparently of the ECHO group but differing from ECHO types 1 to 28. Human thyroid and amnion tissue cultures were considerably more efficient than monkey kidney in isolating the virus.

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2. Committee on the Enteroviruses. *Amer. J. publ. Hlth*, 1957, **47**, 1556.
3. Grist, N. R., Duncan, I. B. R. *Hlth Bull.* (Edinburgh) 1960, **18**, 37.
4. Committee on the ECHO Viruses, *Science*, 1955, **122**, 1187.
5. Mogabgab, W. J., Pelon, W. *Ann. N.Y. Acad. Sci.* 1957, **67**, 403.
6. Macrae, A. D. Personal communication. 1960.

New Inventions

A WARNING DEVICE FOR USE IN SURGERY

THE possibility of cardiac arrest or of major arrhythmias occurring in association with cardiac surgery is very real. During operation, when the heart is exposed, it is a relatively simple matter to diagnose and take remedial action, but post-operatively the onset of cardiac arrest is more difficult to detect. The electrocardiograph may be employed to detect such arrhythmias but, without continual medical supervision for periods of up to several days, such monitoring may be of more apparent than real value.

A patient-controlled pacemaker in which the electrocardio signal automatically controls the pacemaker was used by Leatham, Cook, and Davies.[1] This apparatus is so constructed that should cardiac arrest or severe bradycardia occur the electrical pacemaker automatically initiates and maintains a purposeful contraction at a predetermined rate. An alternative to this is the production of a visual or auditory alarm should such an arrhythmia supervene.

Such a device, known as the Cardiac Alarm, has been developed and this communication describes the apparatus and its experimental and clinical trials.

THE INSTRUMENT

It is important that the apparatus and its connections to the patient be as simple as possible bearing in mind the drip tubes, drainage tubes, thermometers and other equally essential apparatus with which the patient is encumbered.

The controlling signal for the Alarm could be derived from various sources all requiring a minimum of connections to the patient—the heart-sounds, the electrical output of the heart, the pulse, or the blood-pressure. One can immediately eliminate the heart-sounds, as there may be extraneous noises interfering with the signal. Each of the other three possibilities have their advantages. A pulse detector similar to that of Bishop [2] or Zenz and Mounts [3] has the advantage of being quickly connected to the patient and it requires only one lead. The level of arterial blood-pressure is also useful and easily monitored, but alterations in blood-pressure need not necessarily accompany changes in heart activity.

Other factors need consideration and it may well be shown that the electrocardio-signal method which has been adopted is not the best in all circumstances. However, in all cardiac surgery it is usual to insert electrocardiograph electrodes at the beginning of the operation. As these electrodes are the source of a signal there is, therefore, no need for further leads or connections to the patient.

A few other considerations have to be taken into account. The most important is that the apparatus must be very simple to operate and require no attention after the initial setting-up procedure is complete. It must also be portable (preferably battery-operated to facilitate transfer from theatre to ward) and compact. It would be preferable to have the instrument quiescent when the normal signal is received and to give an audible warning if an arrest occurs. In this case it is necessary to have adequate facilities to check the satisfactory operation of the instrument, particularly if it is battery-operated.

THE CIRCUIT

A block diagram (fig. 1*a*) shows the technique adopted. The signal from the patient is fed to an amplifier. The amplified signal is then fed to a trigger device which controls relay contact B.1 (shown normally off). If the amplified R wave is adequate to operate the trigger device, contact B.1 is on. If an R wave of a given minimum amplitude is not received within a predetermined time of the previous R wave, B.1 opens and brings on the oscillator.

Two safety devices are incorporated:

Firstly, on switching on (SW.1), the red "battery test" light comes on via relay contact C.1. At the same instant, the current passing through the thermistor V.A. 2002 and the Post Office relay

1. Leatham, A., Cook, P., Davies, J. G. *Lancet*, 1956, ii, 1185.
2. Bishop, C. *Anæsthesia*, 1958, **13**, 329.
3. Zenz, C., Mounts, F. *Amer. med. Ass. Arch. industr. Hlth*, 1958, **17**, 280.

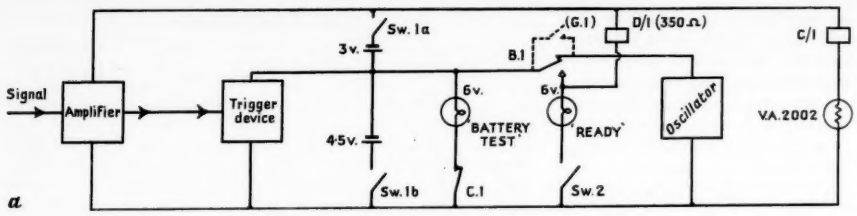

Fig. 1a—Block diagram of the cardiac alarm.

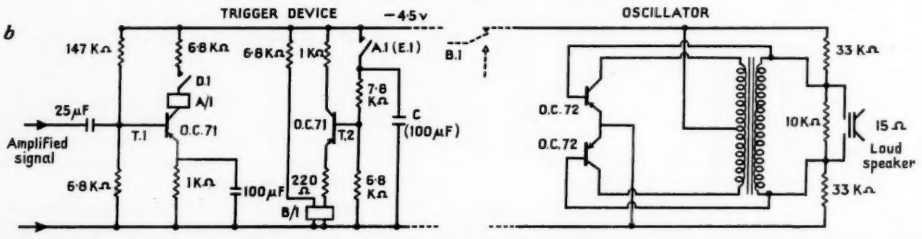

Fig. 1b—The full circuit diagrams of the trigger device and the oscillator. All relay contacts are shown with relays normally off.

C/1 heats the thermistor, thus decreasing its resistance. In a few seconds its resistance is reduced to such a value that sufficient current will pass to bring on C/1. Thus the light goes out. If sufficient current to bring on this relay will not pass (i.e., the red light remains on) the battery should be changed even though the instrument will work for many more hours. Similarly, if the light goes out on first switching on, but later comes on, the battery should be changed.

The second device is a green "ready" light and a spring-loaded, normally open switch SW.2. On pressing this switch the light comes on provided B.1 is on. B.1 will only be on if the device is triggering properly because the relay controlling B.1 is a moving-coil relay in which the common (moving) contact will make with either of the two fixed contacts only if appropriate currents are passing through its coils. The connections to the two coils of this relay are arranged so that B.1 should always bring on either the green light or the oscillator, depending on whether the device is triggering properly or not. The green light is, therefore, a useful check because the instrument is quiescent when working normally and should the power supply fail the instrument will, of course, remain quiescent.

Fig. 1*b* is a circuit diagram of the trigger device and oscillator and a description of the working of the complete circuit follows.

The signal from the patient is fed to an electrocardiograph transistor amplifier. The output of the amplifier is fed to T.1 as shown. If the amplified R wave is of sufficient amplitude T.1 will pass sufficient current to bring on A/1, a 350Ω moving coil relay. Obviously contact D.1 must be closed and, therefore, relay D/1 (fig. 1*a*) must have previously been brought on by pressing the spring-loaded switch. A.1 now charges up condenser C and also alters the bias on T.2 in such a way that sufficient current will pass through the transistor to bring on B/1. After the R wave has passed A.1 opens and the charge on C starts to decay. Before the bias reaches the value at which the current in T.2 allows B/1 to open, the subsequent R wave brings on A/1 as before. Therefore A.1 closes, recharging C and maintaining the current through B/1 which, therefore, remains closed and the green light remains on. On releasing the switch the instrument continues to operate as before. Sometimes, on pressing the switch, the green light flashes. One could interpret this as an indication that an R wave was being received and that each flash corresponded to each R wave. In fact this is not so. The phenomenon occurs very infrequently and is due to the fact that when B.1 opens there is a tendency for the sensitive first stage to trigger the device. This is a similar phenomenon to that described by Kitchen,[4] but has caused no difficulty whatever because if the switch is released when the light is flashing D/1 will be released the instant B.1 opens and D.1 will prevent the device triggering itself off. The oscillator should ring immediately afterwards.

4. Kitchen, L. D. *Electronic Engg*, 1959, **31**, 44.

Thus before the instrument will work it has to be set by pressing the switch and reset after each alarm. If each R wave is amplified to such an extent that it just triggers the device so keeping the oscillator off, we can, by increasing the amplifier gain a given amount, allow for a known and permissible drop in R wave amplitude (say 25%) before the alarm sounds. Also, the heart-rate below which the alarm will sound is set by C and, at present, is of the order of 20 per minute.

RESULTS

After initial tests with an electrocardio-signal simulator, several animal experiments were performed and very encouraging results were obtained. Asystole, ventricular fibrillation, and heart-block were artificially induced many times on a dog and in all cases an alarm was given.

The instrument is now used regularly on all cases undergoing surgery with the assistance of profound hypothermia [5 6] and has been very successful. It is always used in conjunction with a physiological oscilloscope and the leads are connected to the patient, via three needle electrodes, on returning to the ward. In all cases to date the Alarm has behaved perfectly. In most cases it has been used for the first 18 hours or so after operation; no arrests have occurred and no false warnings have been given. Occasionally when the patient has been particularly restless one or two false alarms have been given. This was probably due to the movement of the heart and the resulting change of axis; in one case an electrode was accidentally dislodged. However, such false alarms are readily detected by the presence of an unchanged pulse-rate. In another case, a few hours postoperatively, groups of extra-systoles followed by heart-block occurred at frequent intervals. This was first observed immediately following an alarm. Each subsequent group was similarly detected, which suggests that the first warning corresponded to the first period of heart-block.

VENTRICULAR FIBRILLATION

It will be seen from fig. 2, which is a typical recording taken during the animal experiments, that the amplitude of the R wave is approximately twice the amplitude of the artificially induced fibrillation waves. Therefore, one would expect the alarm to sound in this case, but there may be occasions when the amplitude of the fibrillation waves is greater than the amplitude of the R wave. Unfortunately, such a signal was obtained on

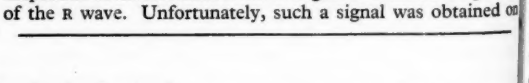

Fig. 2—A recording, taken during the experiments, of a dog's heart (1) beating normally, and (2) in ventricular fibrillation.

The gap in the recording is where the recorder was switched off while fibrillation was induced.

5. Drew, C. E., Anderson, I. M. *Lancet*, 1959, i, 748.
6. Benazon, D. *Anæsthesia*, 1960, **15**, 134.

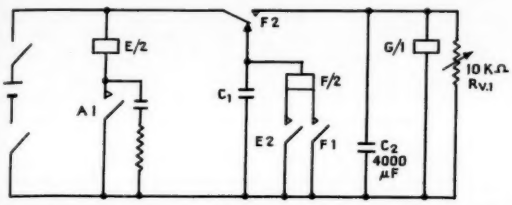

Fig. 3—The circuit diagram of the additional unit for detecting ventricular fibrillation waves of any amplitude. All relay contacts are shown with relays normally off.

only one occasion and the alarm sounded because the amplitude of the fibrillation waves rapidly decreased. It is doubtful, however, whether this will always be the case although the amplitude of ventricular fibrillation waves varies very rapidly and it is likely that, in a large proportion of cases, the alarm would sound within a short time of the commencement of ventricular fibrillation. However, there may be some cases of ventricular fibrillation which will not be detected immediately by the circuit of fig. 1.

Consequently, a small unit has been produced for use with the circuit previously described and this ensures that nearly all cases of ventricular fibrillation will be detected as quickly as possible.

The Circuit

Contact A.1 (fig. 1*b*) now operates a high-speed relay E/2 in the additional circuit (fig. 3). One contact, E.1, replaces A.1. Contact E.2 operates a second high-speed relay F/2 which locks on via contact F.1. Contact F.2 then allows condenser C_2 to be charged up. F/2 is not released and instant the R wave passes because initially the condenser C_1 was charged. Consequently, there is a lag in the release of F/2. Thus the amount of charge that C_2 receives per R wave depends on the length of time that F/2 is held on and is independent of Q-S interval. The total charge on C_2 at any instant depends on the frequency of R waves or, of course, of any wave of sufficient amplitude to trigger the device. The time constant of C_1 and F/2 is 100 msec. and so, with frequencies up to 10 cycles per second, each wave will operate F/2. With frequencies greater than 10 cycles per second alternate waves will be blocked thus producing an effective minimum frequency of 5 cycles per second. Condenser C_2 discharges through moving-coil relay G/1, so arranged that the current passing when the frequency of input waves is 5 cycles per second just closes its normally open contact G.1 (fig. 1), which brings on the alarm. Hence, frequencies of up to 5 cycles per second will be accepted but the alarm will sound for higher frequencies. One could arrange for the alarm to sound at a lower frequency but, in order to avoid false triggering, one should have as large a gap as possible between the highest electrocardio-signal frequency normally encountered, and the triggering frequency. The latter is set by RV.1.

As indicated above, any wave, including the T wave, of sufficient amplitude to trigger the device contributes to the charge on C_2. The effect of the T wave triggering the device is of consequence only if the R-T interval is less than 200 msec. This is equivalent to a frequency greater than 5 cycles per second, in which case the alarm would sound. The minimum amplitude required to trigger the device was previously set by the gain control, usually at approximately 75% of the R-wave amplitude. Should the T-wave amplitude be greater than this, the gain can be decreased until the T wave ceases to trigger the device. A practical limit is a position where the amplitude required to trigger the device is 90% of the R-wave amplitude.

A combination in which the R-wave and T-wave amplitudes are within 10% of each other and in which the R-T interval is less than 200 msec. may occur, however, and so there may be a few cases in which this unit could not be used.

A considerable number of experiments have been performed with this device and an instrument that can be used separately or with the additional unit is under construction. This will be put into regular clinical use as soon as possible.

DISCUSSION

Our experiments have shown that the instrument can be a useful tool and that combined with the additional unit it forms a comprehensive warning device. It may be argued that being imperfect it would be better to use only an electrocardiograph. This entails the constant observation of a pen-recorder trace or oscilloscope spot for many hours or days by medical staff. This is hardly practical and in any case the concentration of the observer would rapidly decrease. In view of the facts that the instrument needs no attention whatever and is simply connected to the patient, it would seem that its use is advantageous, provided one is aware of the limitations previously stressed.

The difficulty of detecting ventricular fibrillation by the method described does not arise if a pulse detector is used because there is no effective pulse during ventricular fibrillation, although there may be some small pulsations. A pulse detector giving an output of the form shown in fig. 4 may be connected to the input of the Alarm. In the event of ventricular fibrillation only a very small output pulse will be obtained from the detector and the alarm will sound. Asystole and heart-block will also be detected. Many experiments have been performed and have shown that the pulse detector has some technical advantages. Extensive clinical trials will be carried out soon.

An instrument giving audible warning of cardiac arrest or of major arrhythmia is of more general application than a patient-controlled pacemaker which instead of giving an audible warning, switches on automatically when the arrhythmia occurs. Also there may be occasional false alarms and harm could be done by triggering the pacemaker when the heart is functioning normally. Therefore, it is considered more satisfactory to have warning of the event so that the patient can be examined and the appropriate action taken. Little time is lost and the human element should always be introduced at such a critical stage. The patient-controlled pacemaker has its place, however, in long-term cases such as treatment of Stokes-Adams attacks. There is however still a danger of false triggering.

Fig. 4—A recording of the output of a simple pulse detector.

Each output pulse, when fed into the circuit of fig. 1, produces the same effect as that of the R wave when the electrocardio-signal is fed into the circuit. When ventricular fibrillation occurs these output pulses are considerably reduced in amplitude and therefore the alarm sounds.

Another application of the Cardiac Alarm is in general anæsthesia. Sudden cardiac arrest occurs from time to time even in minor surgery and the Alarm could be of use in giving an early warning of the event. To be of real value in this application it has to be connected to all patients undergoing surgery. Many clinical trials have been made under these conditions and the instrument has behaved perfectly. Many arguments have been put forward against using the instrument for this purpose, perhaps the strongest being that it is better to have an instrument that warns one of a pending cardiac arrest and not have a warning after the event has taken place. This is true but not in itself a reason for not using the Cardiac Alarm until such times as an instrument of that nature is available. The Cardiac Alarm may well serve a useful purpose in this application.

SUMMARY

A compact battery-operated portable instrument has been developed which, after initial setting up, requires no further attention. It normally remains quiescent but in the event of asystole or heart-block occurring an audible warning is given. A similar audible warning is given in a large proportion of cases of ventricular fibrillation. Various facilities to test the battery and the satisfactory operation of the instrument are provided which are used occasionally when the instrument is in use for long periods. An additional circuit, that can be incorporated in

the instrument or simply connected to it as required, to detect all cases of ventricular fibrillation has also been developed.

It can be seen that the Cardiac Alarm has many potentialities. In its present form it has several limitations. It may be readily modified to utilise the pulse instead of the electrocardio signal by using a simple pulse detector. It is, however, speculative whether a device based on the pulse or on the blood-pressure would be a great improvement. A combination of electrocardio-signal, pulse, and blood-pressure in coincidence may also be useful, but such an apparatus is better suited to the experimental laboratory than the ward. Work is continuing but the present apparatus is very satisfactory. It has been most useful in the postoperative care of patients undergoing cardiac surgery at Westminster Hospital.

I am greatly indebted to Mr. C. E. Drew and the members of his team, particularly Mr. G. Keen and Dr. D. Benazon, for their continual advice and help. Dr. C. W. Wilson, chief physicist, has readily given advice and encouragement throughout this project. The instrument was developed from an idea of Mr. E. Stanley Lee, who has given unfailing encouragement and help.

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Reviews of Books

Modern Scientific Aspects of Neurology

Editor: JOHN N. CUMINGS, M.D., F.R.C.P., professor of chemical pathology, Institute of Neurology, University of London. London: Edward Arnold. 1960. Pp. 360. 65*s*.

THIS monograph comprises ten essays by British and Continental authors on various questions basically related to neurology. Of the ten, six are on biochemical themes—the nucleic acids of nerve-cells, two on the lipidoses, the histochemistry of demyelination, the lipids of normal brain, and the esterases of the nervous system. Two more are concerned with the structure of the myelin sheath as disclosed by X-ray diffraction methods and electron microscopy. The remaining two deal with nerve-endings in skeletal muscle and the physiopathology of epilepsy and the convulsive state.

There is now a good deal of work in progress, much of it biochemical, on the fundamentals of neurology, and this book admirably summarises some of the more actively growing areas. It is from them—and from kindred fields of experimental pathological research—that the much-needed renaissance in neurology is most likely to come. How far the editor's hope "that the practising neurologist may obtain new information which is related to his work" will be fulfilled will depend upon whether neurologists are prepared to follow the example of active clinicians in other specialties and seek contact with modern scientific work underlying their particular part of medicine.

The production is good, though in one or two contributions the translation might have been smoother. The articles are well documented (over 1500 references) so that the monograph also provides a useful source of first-hand information for research-workers.

Laboratory Technique for the Study of Malaria

PERCY G. SHUTE, M.B.E., F.R.E.S., MARJORIE E. MARYON, F.R.E.S., Malaria Reference Laboratory, Horton, Surrey. London: J. & A. Churchill 1960. Pp. 86. 10*s*. 6*d*.

THIRTY-THREE years ago the Ministry of Health established a laboratory in Horton to assist in the treatment of neurosyphilis by malaria therapy. Mr. Shute was in charge, and for the past twenty years has been assisted by Miss Maryon. Since the inception of this unit some 100,000 mosquitoes have been used, and the experience of the authors in laboratory techniques for the study of malaria must be unequalled. This concise book has four sections describing preparation and staining of blood-films; laboratory procedures for demonstrating the diverse malarial parasites in all their stages; care of the anopheles in the laboratory; and six pages of invaluable practical "hints". "Thick and thin films will stain perfectly up to at least 3 years if kept in a desiccator which is stored in a domestic refrigerator." "A more even thick film is obtained if the blood is distributed on the slide to form a square . . ." "Anisol is satisfactory (as a substitute for cedar immersion oil) . . . it does not harden on the slide and a drop disappears in about 20 minutes."

There is a selected bibliography in chronological order in which the authors' names appear with many collaborators—among them the late Colonel S. P. James and Sir Gordon Covell (who contributes a foreword). One reference cites the classical paper by Shortt, Hamilton Fairley, Covell, Shute, and Garnham on "the pre-erythrocytic stage of *Plasmodium falciparum*". The Wellcome Museum has contributed most of the 24 excellent photographs.

Dr. Kelly of Hopkins

AUDREY W. DAVIS. Baltimore: Johns Hopkins University Press. London: Oxford University Press. 1959. Pp. 242. 40*s*.

Johns Hopkins is unique amongst famous hospitals in that it did not grow gradually or attain its illustrious status over many decades. Instead, it sprang into being full size, from the benefaction of a wealthy Quaker: and within a few years the work of four men had made its name familiar and respected all over the world. Of those four men, William H. Welch was renowned before he went to Baltimore, while Osler is the subject of what is probably the finest medical biography ever published. Very few writers on the recent history of surgery have failed to discuss at length the brilliant, eccentric, and pathetic figure of Halsted. Only in the case of Howard A. Kelly has, until now, a full-length study been lacking; and therefore this book, by one who was his close personal friend for over twenty years, is assured of a wide sale.

Miss Davis has subtitled her book Surgeon: Scientist: Christian, and indeed the impression that emerges from it is of a man who led simultaneously three very full lives. As a surgeon, Kelly achieved a notable reputation, and considerable wealth, by establishing early in his career one of the first clinics in the United States devoted to diseases of women. His scientific enthusiasms were principally for mycology and herpetology, and to visit his home was often to risk a disconcerting encounter with some formidable-looking snake. Throughout his life, he was moved by strong militant and evangelical religious convictions which, as he himself acknowledged, sometimes set him apart from his colleagues. Yet if Kelly allowed his religious zeal to intrude into his professional activities, the reverse was also true; for it is typical of his thoroughness, and generosity, that throughout those years when his income was at its highest, he would start his accounting each month by setting aside a fifth of the fees and the salary he had received, to be used for charitable purposes.

Essentials of Fluid Balance (2nd ed. Oxford: Blackwell Scientific Publications. 1960. Pp. 135. 20*s*.).—In the three years since it first appeared, Prof. D. A. K. Black's introduction to the problems of fluid balance has become widely known, and the new edition will be welcomed by students and teachers. The references are again up to date, and as before Dr. Black follows the praiseworthy trend of including the titles of papers he cites. This feature is particularly important for the non-specialist for whom the book is designed. Changes in the text are relatively small, but the only disappointment is not to find a more radical approach to the problems of acid-base balance. The production is excellent, at a price even the student can afford.

Surgery of Repair as applied to Hand Injuries (2nd ed. Edinburgh: E. & S. Livingstone. 1960. Pp. 284. 45*s*.).—In the second edition of this book by Mr. B. K. Rank and Mr. A. R. Wakefield, of Melbourne, no major change has been necessary, and the chapter headings are the same. There have been minor additions to the text and the illustrations, which are of outstanding quality and a supplementary lesson in themselves. This book should certainly be in the possession of all who are called upon to treat hand injuries.

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Tropical Diseases in Britain

Now that Africa is accepting the civilisation of Western Europe, and is trying to adapt it to African needs, there is more exchange between Africa and Europe than ever before. Until a few years ago such exchange was mainly commercial; but now the most numerous exchanges are of teachers and students; and our visitors from Africa, or from parts of the world largely peopled by Africans, such as the Caribbean islands, include some who settle in this country to raise a family. Migrants may bring with them inherited metabolic peculiarities which, in their original environment, were either advantageous or neutral but which in the new environment may be neither. Such, for example, is the record of sickle-cell disease in Portugal, where it was introduced about three hundred years ago from West Africa; while in Sicily and Greece this disorder was probably introduced much earlier. In Britain we are now discovering that the differential diagnosis of hæmoglobinopathies is important in all large cities; for immigration from Africa, the West Indies, Italy, Cyprus, and Greece is considerable.

But immigration today is chiefly for shorter periods: students and workers come from Ghana, Guiana, Trinidad, or the Cameroons; beauty queens from Jamaica or Nigeria; film starlets from the Ivory Coast or from Martinique. They come, not by the old, slow surface transport, but by air, and they bring with them infective diseases, especially those with long incubation periods or no very obvious clinical manifestations. Thus the anæmic Trinidadian lad may have hookworm, and the chronic urticaria which has plagued the schoolteacher since his return from West Africa may be caused by the microfilaria *Acanthocheilonema perstans* in his blood—even though the textbooks unite in saying that this filaria is non-pathogenic.

The commonest and most important of tropical diseases is malaria, and we are getting our share of it. Benign tertian malaria due to *Plasmodium vivax* is often with us, usually as relapses after inadequate treatment. Fortunately, as this common form is self-limiting, even though relapses are usual, an error of diagnosis is unlikely to be fatal. This, however, is very far from true of malignant tertian malaria due to *P. falciparum*, which not only is often fatal but also is clinically more protean than is the benign infection with *P. vivax*. Benign tertian malaria usually produces paroxysms of ague; malignant tertian may produce regular or irregular fever of any severity, and collapse with subnormal temperature, vomiting, and diarrhœa—or even, after a fever of quite short duration, the rapid onset of confusion and coma. Further, the plasmodia are sometimes difficult to find in blood-films; and in one case recently no parasites could be found in the peripheral blood on six occasions, though they were readily discovered in the bone-marrow.

Clearly in the differential diagnosis of pyrexia of undetermined origin the recent travels of the patient constitute a most important guide. At least one patient has lately died from malignant tertian malaria because too little notice was taken of his journeys and the diagnosis was made too late. If a patient with fever of unknown origin has recently been in a malarious area (such areas should be taken to include all Africa, most of Asia, including India and Burma, much of the Mediterranean littoral, and the Americas between the tropics), then his fever should be presumed to be due to malaria until this has been disproved—if need be, by a therapeutic test. Treatment may reasonably be deferred until an attempt has been made to verify the diagnosis; but in this country, if the history and the clinical manifestations suggest malaria, a diagnostic therapeutic test is desirable even when no parasites can be found in the peripheral blood. The experts on tropical medicine may claim that any competent microscopist will find plasmodia in the peripheral blood when fever is due to malaria; but in Britain this is not always true, especially in primary infections with *P. falciparum* or relapses of infections with *P. vivax*. Symptomless infections with *P. falciparum* are not rare among those who have lived on the West Coast of Africa; and in an article on p. 469 of this issue Dr. GRANT and his colleagues discuss the implications of this in relation to blood-transfusion. Clearly the use of blood from a donor who has spent much of his life in West Africa may be dangerous to the recipient; and the development of a fever of uncertain origin within a few weeks after blood-transfusion should henceforward raise a suspicion of malaria.

Other infections, once thought to be exclusively tropical, are now appearing. Returned Servicemen or holiday-makers may develop the hectic fever of Mediterranean leishmaniasis (kalar-azar), another disease not usually encountered in England but fairly easily diagnosed by the positive serum flocculation tests (Kunkel, thymol, Sia) and leucopenia; but so far we are spared Oroya fever (bartonella infection) and Chagas' disease (Brazilian trypanosomiasis), though the latter will probably appear fairly soon. Just now, malaria from Africa is the great danger, and this will be controlled only when every practising doctor thinks of the possibility and takes a history of travels abroad.

Body-temperature and the Emotions

IF malingering is excepted, fevers attributed to psychological causes fall roughly into three categories. Firstly, body-temperature may be raised during excitement, anxiety, or distress. This, though well known to happen in children, is usually regarded as unusual in adults. We clearly need more information about the extent to which body-temperature can be influenced by acute emotional stress [1–3]; and a step in this direction has been taken by RENBOURN,[4] who studied the temperatures of

1. Malleson, N. *Lancet*, 1959, i, 225.
2. Goodall, J. W. D. *ibid.* p. 631.
3. Sheldon, D. W. S. *ibid.* p. 835.
4. Renbourn, E. T. *J. psycho-som. Res.* 1960, **4**, 149.

schoolboys and young men engaged in amateur boxing competitions. He measured the mouth-temperatures of boys aged 12–14 immediately before they boxed in competitions, and compared these with temperatures taken in the same way, and at the same time of day, either at home or before training exercises. The average temperature of 12 boys before competitions was 99·9°F —1·4°F higher than that in quiet circumstances at home. Temperatures of up to 101°F were recorded.

The temperature before training bouts was lower, but still about 0·5°F higher than the temperature at home. In a series of training sessions, the boys' temperatures tended to decline: this was not related to environmental conditions. No such acclimatisation was found during a series of competitions, and RENBOURN suggests that the temperature elevation was related to the excitement and the uncertainty of the outcome.

The temperatures of boys before competition bouts were about 1°F higher than those of members of the audience, though at one particularly exciting meeting there was no significant difference. Surprisingly, the pulse-rate was almost totally insensitive to the stimuli which affected oral temperature, and the boxers' pulse-rates did not differ from those of the audience. Similar comparisons between the temperatures of 24 young adult boxers and 21 members of their audience showed that the average temperature of the boxers was 0·5°F higher than that of the audience, though their pulse-rates did not differ significantly. A similar temperature difference was found between participants and spectators during an athletic contest. RENBOURN's work tends to confirm the belief that, with increasing age, emotional stimuli are less likely to cause elevation of temperature, though information about the response of older persons is lacking.

The mechanism of these temperature changes is unknown. The contestants had not performed any strenuous exercise before their temperatures were taken, but unconscious movements and increased muscle tone may have played a part: the only evidence tending to discount this was the absence of tachycardia. The release of adrenaline, which is known to occur in situations of this kind, may have played a part.

It is perhaps surprising that relatively few patients attending outpatient clinics are found to have temperatures raised without clear cause. Perhaps the explanation may lie in the methods used for taking temperatures. RENBOURN left the thermometer in place for five minutes; but oral temperatures are seldom measured for this time in the clinic, and shorter measurements will slightly underestimate the temperature.

In the other two categories, the fever has been attributed to psychological factors more tentatively, for the relation to emotional stress is much less clear. In the first of these two the elevation of temperature, which is usually modest, may last for years.[5] The condition is commoner in women than in men; and the temperature is unaffected by salicylates, though it may be reduced by morphine. In women, the temperature is influenced by ovulation. Patients in this group may simply represent the extreme upper limit of a normal frequency distribution; and many are unlucky in that they are submitted to extensive investigation, and all the anxiety that this may induce. Of 100 such patients reported by ROWNTREE and KINTNER,[6] 7 were eventually found to have organic disease. In 55 of the patients, the temperature returned to normal months or years later. Such patients are sometimes considered to be neurotic; but possibly their neurosis is induced by the discovery of a raised temperature, and the case for regarding this condition as of emotional origin is weak.

The other type of fever for which a psychological cause has been tentatively suggested is periodic fever. In this condition, without other evidence of disease, bouts of high fever, lasting up to a week at a time, recur at intervals of weeks or months; the condition may be life-long, and has been observed in more than one member of a family.[7 8] Salicylates usually depress the fever, though in at least one patient, who had electro-encephalographic abnormalities, they were ineffective.[9] Faute de mieux, there has been a tendency to blame the psyche for this condition, but its acquittal may be heralded by the findings of BONDY et al.[10] These workers discovered unconjugated ætiocholanolone in the plasma of 2 patients with this condition, during febrile episodes, but not when they were afebrile. Ætiocholanolone, as well as certain other steroids, has been found to cause fever in man, though not in rabbits.[11] In man, it is more powerfully pyrogenic when given intramuscularly than when given intravenously, and its injection causes considerable local irritation; whether the pyrogenic effect is secondary is not yet clear. BONDY et al. suggest that the finding of unconjugated ætiocholanolone in plasma indicates an episodic failure of conjugation by the liver, rather than an abnormality of steroid secretion. In view of the known depression of liver functions during pyrogen-induced fever,[12] it is still difficult to distinguish cause from effect; but these observations, if confirmed, may be very important.

The Circulating Cancer Cell

SPREAD of cancer by the blood-stream has long been known, but we have been slow to act on this knowledge: attention has been focused more on the source of the cancer cells and the points to which they are distributed than on their lines of communication—an oversight of which no good strategist would be guilty.

It is all but a century since ASHWORTH[13] recorded his observation of cells in the blood-stream resembling those of a multifocal skin tumour. Following similar desultory observations by others in the living,[14] the dying,[15] and the dead,[16] POOL and DUNLOP[17] with prognosis in mind made a determined effort to ascertain whether

5. Reimann, H. A. *J. Amer. med. Ass.* 1936, **107**, 1089.

6. Rowntree, L. G., Kitner, A. R. *Trans. Ass. Amer. Phycns*, 1933, **48**, 60.
7. Reimann, H. A. *J. Amer. med. Ass.* 1948, **136**, 239.
8. Wolf, S., Wolff, H. G. *Arch. intern. Med.* 1942, **70**, 293.
9. Naeye, R. L. *Ann. intern. Med.* 1958, **48**, 859.
10. Bondy, P. K., Cohn, G. L., Herrman, W., Crispell, K. R. *Yale J. Biol. Med.* 1958, **30**, 395.
11. Kappas, A., Soybel, W., Glickman, P., Fukushima, D. K. *Arch. intern. Med.* 1960, **105**, 701.
12. Bradley, S. E., Conan, N. J. *J. clin. Invest.* 1947, **26**, 1175.
13. Ashworth, T. R. *Aust. med. J.* 1869, **14**, 146.
14. Schleip, K. *Z. klin. Med.* 1906, **59**, 261.
15. Ward, G. R. *Lancet*, 1913, i, 676. Marcus, H. *Z. Krebsforsch.* 1917, **16**, 217.
16. Aschoff, L. *Münch. med. Wschr.* 1906, **53**, 337. Quensel, U. *Uppsala LäkFören. Förh.* 1921, **26**, 1.
17. Pool, E. H., Dunlop, G. R. *Amer. J. Cancer*, 1934, **21**, 99.

cancer cells could be identified in the blood of patients. They took 5 ml. samples of blood from 40 patients with advanced neoplasms at sites varying from breast to alimentary tract and found malignant cells in 17. More recently COLE et al.[18] demonstrated malignant cells in the venous perfusate of malignant neoplasms removed at operation; and FISHER and TURNBULL[19] recovered malignant cells by venous perfusion of the lesion in situ in 8 of 25 cases of large-bowel neoplasm. These experiments were undertaken in order to show the dangers of spread by manipulation. ENGELL,[20] in a larger investigation involving 140 patients, found no evidence for the view that manipulation might increase the danger of cellular escape via the blood-stream, even though tumour cells were found in the venous blood draining the tumour area in 63 of 107 cases of large-bowel cancer. He detected cancer cells in the peripheral blood both during operation and in advanced inoperable cases; but he concluded that these had neither prognostic nor diagnostic value, though hæmatogenous spread was apparently related to the histological grade of the tumour. MOORE et al.[21] reported positive findings in the peripheral blood of 93 of 179 cases, in many of which the primary lesion was situated on the portal system. COLE et al.[22] found that the more advanced the lesion the likelier were cancer cells to be present in the blood; that operative manipulation of the lesion apparently increased the number of cells circulating; and, in 2 cases, that within minutes of removal of the primary lesion cancer cells disappeared from the circulation. The simple diagnostic manœuvre of uterine curettage could cause cancer cells to appear momentarily in the caval blood of patients with a growth involving the endometrium.[23] DELARUE[24] found cells still circulating in the postoperative period after an increase in the number during removal of neoplasms of lung, bowel, and breast; and his associates[25] found such cells in the blood for up to nine days after operation in 63% of their cases. Cancer cells were present in the peripheral blood of 11% of COLE's curable cases (7 patients out of 66) and in 31% of the incurable (8 out of 26), and with a simplified technique these proportions have risen to 25% and 39% respectively.[26]

The problem of the fate of the freely circulating cancer cell is like that of the fly in winter-time. MOORE et al.,[27] who have shown a direct correlation between vein invasion and the presence of free cells in the regional venous effluent, state that probably 99·9% of all tumour cells reaching the circulation fail to survive. This claim is supported by only circumstantial evidence —namely, that malignant cells are often to be found in the peripheral blood of patients with cancer (and the techniques of blood-sampling at our disposal are such that the published figures almost certainly err on the low side), whereas clinically the incidence of metastases is lower than might be expected from the frequency of positive blood findings. Why, then, should some cells or clumps of cells survive and others not? It is difficult to be sure that all the cells in the blood-stream which appear to be malignant are in fact so; reinjection does not always reproduce the tumour,[28] though successful experimental implants[29] and tissue culture[30] have been reported. Furthermore, why do some tissues appear to make better hosts than others? Malignant cells in the peripheral circulation should provide fairly uniform delivery to all tissues; yet this is contrary to the clinical evidence of the distribution of metastases. The answers must be complex since many factors, both physical and biochemical, come into play—tumour-cell size in relation to vascular lumen, blood-supply, and host tissue-metabolism in relation to tumour-cell needs, to mention only a few. In a Hunterian lecture, GRIFFITHS[31] reported that both stress and catabolic disturbance have been shown experimentally to increase host susceptibility to the tumour-cell.

Meanwhile, in expectation of this fundamental knowledge, the attack on the lines of communication has started, as so often in medicine, in an empirical way. Dakin's solution, actinomycin D, alkylating agents such as nitrogen mustard (mechlorethamine), antimetabolites such as 6-mercaptopurine, agents which inhibit mitosis such as desacetylmethylcolchicine, and other tissue poisons—all have been used, sometimes by perfusion.[32] The advantage of chemotherapy is that it may affect not only the primary source[33] but also cells free in the circulation. COLE has taken the logical step of injecting mechlorethamine into the portal circulation at the time of excising a gastrointestinal neoplasm[34]; some of the solution is left in the peritoneal cavity, not only to destroy exfoliated cells there, but also to permit absorption into the systemic circulation. Depression of the bone-marrow is avoided by careful dosage. This is less easy in the large open wounds associated with radical mastectomy or cervical lymph-node dissections. In such cases a 1% solution of monoxychlorosene ('Clorpactin XCB') has been tried; but it proved relatively ineffective in this concentration and too toxic in a 2% solution. COLE et al.[35] have now turned to Dakin's solution. They use 0·5% sodium hypochlorite, which must be buffered with sodium bicarbonate to avoid toxicity; wounds are irrigated with this solution for from one to four minutes before closure. At this empirical stage the chief problem of chemotherapy for cancer is how to avoid damage to normal tissue.

18. Cole, W. H., Packard, D., Southwick, H. W. *J. Amer. med. Ass.* 1954, **155**, 1549.
19. Fisher, E. R., Turnbull, R. B. *Surg. Gynec. Obstet.* 1955, **100**, 102.
20. Engell, H. C. *Acta chir. scand.* 1955, suppl. 201.
21. Moore, G. E., Sandberg, A., Schubarg, J. R. *Ann. Surg.* 1957, **146**, 580.
22. Roberts, S., Watne, A., McGrath, R., McGrew, E., Cole, W. H. *Arch. Surg., Chicago*, 1958, **76**, 334.
23. Roberts, S., Long, L., Jonasson, O., McGrath, R., McGrew, E., Cole, W. H. *Surg. Gynec. Obstet.* 1960, **111**, 3.
24. Delarue, N. C. *Canad. med. Ass. J.* 1960, **82**, 1175.
25. Salgado, I., Hopkirk, J. F., Long, R. C., Ritchie, A. C., Webster, D. R. *ibid.* 1959, **81**, 619.
26. Long, L., Jonasson, O., Roberts, S., McGrath, R., McGrew, E., Cole, W. H. *Arch. Surg., Chicago*, 1960, **80**, 910.
27. Moore, G. E., Sandberg, A. A., Watne, A. L. *J. Amer. med. Ass.* 1960, **172**, 1729.
28. Taylor, F. W., Vellios, F. *Surgery*, 1958, **44**, 453.
29. Grove, W. J. *Arch. Surg., Chicago*, 1959, **78**, 698. Jonasson, O. Communication to American College of Surgeons, 1958.
30. Moore, G. E., Mount, D. T. *ibid.*
31. Griffiths, J. D. *Ann. R. Coll. Surg. Engl.* 1960, **27**, 14.
32. Creech, O. J., Krementz, E. T., Ryan, R. F., Reemtsma, K., Elliot, J. L., Winblad, J. N. *J. Amer. med. Ass.* 1959, **171**, 2069.
33. Hurley, J. D., Hall, F. M. *Arch. Surg., Chicago*, 1960, **80**, 928.
34. Collier, R. G., Ey, R. C., McDonald, G. O., Cole, W. H. *ibid.* 1959, **78**, 528.
35. McDonald, G. E., Gines, S. M., Cole, W. H. *ibid.* 1960, **80**, 920.

Annotations

EMPLOYMENT PROBLEMS OF HANDICAPPED YOUTH

STUDIES on the adolescent period of life, particularly psychological and social aspects, were formerly much neglected.

In the past ten years the researches of Professor Ferguson and his colleagues in the department of public health and social medicine, University of Glasgow, have provided a great deal of valuable information. *The Young Wage Earner*,[1] *Employment Problems of Disabled Youth in Glasgow*,[2] *The Young Delinquent in his Social Setting*,[3] and *In Their Early Twenties*[4] are now followed by *Handicapped Youth*.[5] Here Ferguson and Kerr describe a study of 1000 handicapped young people in the post-school years: 600 had a physical handicap, which was often complicated by severe educational retardation; 400 had attended special schools for the mentally handicapped. Two groups of physically handicapped young people were studied: a group with cardiac disease considered to be in need of vocational guidance; and a group with a wide range of other physical handicaps that were regarded as likely to prejudice employment. All were studied and given advice before leaving school and for two years afterwards. These two groups were studied separately because it soon became apparent that their problems were fundamentally different.

Those handicapped by cardiac disease were found to have derived considerable benefit from vocational guidance, when compared with a similar group to whom no advice was given. The proportion unemployed two years after leaving school was 7%, compared with 16% in the control group; while 28% were in semiskilled or unskilled work, compared with 49% of the controls. Surprisingly, those with other forms of physical handicap were found to have derived no benefit from vocational guidance when compared with a control group. The explanation is to be found in the fact that the group with physical disabilities other than cardiac conditions had more serious basic disadvantages than the cardiac group. Most of them had been disabled at an earlier age and had therefore lost more schooling, and a far higher proportion had been educated in special schools for the physically handicapped. Moreover, this group came from a poorer home background. It was not surprising therefore that the performance of these young people after leaving school was inferior to that of the " cardiac " group. The proportion unemployed two years after leaving school was 17%, compared with 7% in the "cardiac " group; while 44% had lost three months or more of working time, compared with 18% of the " cardiacs ". The proportion in semiskilled or unskilled work was much higher in this group (55%) than in the " cardiac " group (27%). This shows how much more important early concentration on social and educational factors is than vocational guidance given to less well habilitated children shortly before or just after leaving school.

Mentally handicapped young people who had been educated in special schools were visited in their homes when they were in their early twenties, in order to find out how they had fared since leaving school and how far their subsequent performance had been influenced by social background and limited scholastic ability. The team was amazed to find that they had been so successful in holding jobs with such meagre educational equipment, and often without the advantage of a good home and stimulating parents; for the great majority had remained in steady employment, some into their middle twenties. But the general social condition of many of these young people left much to be desired. Many of our young criminals are recruited from the ranks of high-grade mental defectives; and no less than a third of educationally retarded lads had been convicted on one or more occasions —twice the figure for a control group—and half these convictions were between the ages of 17 and 25 years. Half of those who were unemployed had been convicted. There is clearly an urgent need for much more preventive care to be given to high-grade mental defectives.

Ferguson and Kerr observe that it is perhaps inevitable that such efforts to improve the prospects for handicapped youth should be heavily tinged with disappointment, yet many of those studied were outstandingly successful in overcoming the difficulties arising not only from their basic handicaps but also often from environmental circumstances. The authors rightly remark that " There is a point where, if scholastic ability and home environment are poor enough, it is extremely difficult to influence favourably the performance of a physically handicapped child ": beyond doubt closer attention to the social and educational aspects earlier in childhood would improve the results. Few will disagree with the conclusion that " Handicapped youth is probably the group in the population which, above all others, will repay time and effort spent upon it. In making such efforts we will not only reduce the long-term economic liability which many of these young people are apt to represent, but find a line of approach to some of the major social problems of our time ".

ANALOGUES OF ANTIBIOTICS

A REPORT on the red dye, 'Prontosil', by Domagk[1] in 1935 was followed by the demonstration that its activity depended on sulphanilamide, and analogues with a wider antibacterial range were soon developed. Additions to the list included readily absorbed oral and parenteral forms, poorly absorbed or " gut-active " forms, and more recently the long-acting varieties. A similar trend has followed the introduction of the antibiotics. Crystalline benzylpenicillin has been followed by procaine, benethamine, benzathine, allylmercaptomethyl, and phenoxymethyl penicillins; while dihydrostreptomycin was produced by catalytic hydrogenation of streptomycin.

A whole family of tetracyclines is now in common use. Chlortetracycline was isolated from *Streptomyces aureofaciens* in 1948[2] and oxytetracycline from *Streptomyces rimosus* in 1950[3]; and in 1953[4,5] independent groups of workers simultaneously produced the basic drug

1. Ferguson, T., Cunnison, J. The Young Wage-Earner. London, 1951.
2. Ferguson, T., MacPhail, A. N., McVean, M. I. Employment Problems of Disabled Youth in Glasgow. Medical Research Council memorandum no. 28. H.M. Stationery Office, 1952, see *Lancet*, 1952, ii, 120.
3. Ferguson, T. The Young Delinquent in His Social Setting. London, 1952.
4. Ferguson, T., Cunnison, J. In Their Early Twenties. London, 1956.
5. Ferguson, T., Kerr, A. W. Handicapped Youth: a report on the employment problems of handicapped young people in Glasgow. London: Oxford University Press for the Nuffield Foundation. 1960. Pp. 147. 15*s*.

1. Domagk, G. *Dtsch. med. Wschr.* 1935, **61**, 250.
2. Duggar, B. M. *Ann. N. Y. Acad. Sci.* 1948, **51**, 177.
3. Finlay, A. C., Hobby, G. L., P'an, S. Y., Regna, P. P., Routien, J. B., Seeley, D. B., Shull, G. M., Sobin, B. A., Solomons, I. A., Vinson, J. W., Kane, J. H. *Science*, 1950, **111**, 85.
4. Boothe, J. H., Morton, J., Petisi, J. P., Wilkinson, R. G., Williams, J. H. *J. Amer. chem. Soc.* 1953, **75**, 4621.
5. Conover, L. H., Moreland, W. T., English, A. R., Stephens, C. R., Pilgrim, F. J. *J. Amer. chem. Soc.* 1953, **75**, 4622.

tetracycline. These three tetracyclines have similar pharmacological and antibacterial properties, dosage, and complications. Indeed, their close chemical similarity robs them partly of therapeutic distinctiveness. A recent addition to the tetracycline family is demethylchlortetracycline, produced by a mutant strain of *Streptomyces aureofaciens*.[6] Owing to its slower renal excretion,[7] it provides higher and more sustained antibacterial activity in the serum than its analogues.[8 9] Judged by in-vitro susceptibility of 861 strains of 15 different species of human pathogenic bacteria, demethylchlortetracycline was the most active tetracycline analogue, or as active as any other, against two-thirds of all strains; whereas chlortetracycline was more active against some gram-positive organisms, and tetracycline was more active against some resistant strains of staphylococci.[10]

Chemical manipulations are also changing the face of erythromycin, first isolated in 1952 [11] from *Streptomyces erythreus* and now a well-established alternative to penicillin, notably in the treatment of staphylococcal infections, and also indicated, in conjunction with antitoxin, in the management of diphtheria. Higher blood levels, prolonged tissue concentrations, satisfactory clinical responses, and absence of toxicity are now claimed for propionyl erythromycin lauryl sulphate.[12 13]

The clinician endeavouring to keep abreast finds difficulty in deciphering new names, official and otherwise, which may relate to new antibiotics, to combinations of them, or to fresh analogues. Bewildered also by new dosage schedules, he is likely to retreat to the safety of his older, well-tried favourite. Commercial firms evidently recognise his dilemma; for, despite the advantages of the latest, they continue to produce its predecessors in deference to continuing demand. This is quite unlike consumer demand in other industries. Few men would prefer a 1950 to a 1960 motor-car, and fewer housewives would willingly choose a mark-1 washing-machine when its mark 4 is already on the market.

If the increasing chaos is to be abated, the medical profession and the pharmaceutical industry will have to work still more closely together. Controlled clinical trials will define the relative merits of some agents. Last week, for instance, Dr. Fairbrother and Dr. Taylor [14] described a comparative trial of penicillins G and B.

ANTISTREPTOLYSIN AND RHEUMATIC FEVER

ACCEPTANCE of the causal association between hæmolytic streptococcal upper-respiratory infections and acute rheumatism rests largely on serological evidence; but Lawy [15] declares that this evidence is being differently interpreted by different workers.

In the past thirty years reports from many parts of the world have shown with cumulative force that during an acute attack of rheumatic fever antibodies against one or more of the known antigens of group-A β-hæmolytic streptococci appear in the patient's serum in high or rising titre. This response is specific, and denotes recent infection with these organisms. The antibody which has received most attention is that directed against streptolysin O—a soluble hæmolysin produced by streptococci of this group. Determination of antistreptolysin O (A.S.O.) has become a yardstick of streptococcal infection since Todd's original work [16] with this antigen-antibody system. Finding streptolysin O antigenic, he devised a method for titrating A.S.O. which in convenience and reproducibility has not been superseded by methods introduced later for detecting antibodies to other streptococcal antigens.

Todd, having shown that A.S.O. responses were specifically related to hæmolytic streptococcal infections, went on to study A.S.O. in rheumatic fever, whose association with streptococcal infection had been stressed by Coburn.[17] He found that, whether or not a bacteriologically proved hæmolytic streptococcal infection was observed before the onset, the sera from patients with rheumatic fever showed raised or rising A.S.O. titres as often as the sera of patients recovering from uncomplicated streptococcal infections. Lawy draws attention once again to the frequency of rise in A.S.O. titre after streptococcal infections—namely, about 80%. If antibodies to other streptococcal antigens (streptokinase, hyaluronidase) are included, the figure for serological response approaches 100%.

The pattern of the A.S.O. response in rheumatic fever has also been extensively studied. Some of the features believed by earlier workers to represent a response characteristic of rheumatic fever have not been substantiated. Magnitude of response, for example, is not related to severity of attack, nor persistence of titre to chronicity.[18] It has been repeatedly confirmed, however, that the antibody response is usually somewhat higher in rheumatic fever than in non-rheumatic streptococcal infection.[19] This corresponds to Stetson's finding [20] that the attack-rate of rheumatic fever after streptococcal infection is higher in individuals showing a greater antibody response. This effect may be associated with repeated streptococcal infection, which, as Rantz [21] has shown, leads to the early development of an enhanced antistreptococcal response in childhood. But, although in rheumatic fever additional enhancement usually seems to occur, this is not an invariable, or even a diagnostically useful, feature. For example, Holborow and Isdale [22] found that in very young children with acute rheumatism the A.S.O. titre may be significantly less raised, and less often raised, than in children 8–10 years old.[22]

In general, the test is clinically useful mainly in detecting the imprint of recent streptococcal infection, especially when bacteriological evidence is lacking. In initial attacks and recurrences of rheumatic fever positive serological findings are useful, and in the long-term management of cases negative tests at intervals provide a check on the efficacy of antibiotic prophylaxis against streptococcal infections. As Lawy has found, the A.S.O. test may also be useful in another non-suppurative complication of streptococcal infection—acute nephritis.

6. McCormick, J. R. D., Sjolander, N. O., Hirsch, U., Jensen, E. R., Doerschuk, A. P. *ibid.* 1957, **79**, 4561.
7. Kunin, C. M., Dornbush, A. C., Finland, M. *J. clin. Invest.* 1959, **38**, 1950.
8. Kunin, C. M., Finland, M. *New Engl. J. Med.* 1958, **259**, 999.
9. Hirsch, H. A., Finland, M. *ibid.* 1959, **260**, 1099.
10. Hirsch, H. A., Finland, M. *Amer. J. med. Sci.* 1960, **239**, 288.
11. McGuire, J. M., Bunch, R. L., Anderson, R. C., Boaz, H. E., Flynn, E. H., Powell, H. M., Smith, J. W. *Antibiot. Chemother.* 1952, **2**, 281.
12. Reichelderfer, T. E., Baird, R. L., Ossofsky, H. J. Antibiotics Annual 1959–60; p. 899.
13. Anderson, R. C., Lee, C. C., Worth, H. M., Harris, P. N. *J. Amer. pharm. Ass.* scientific edition, 1959, **48**, 623.
14. Fairbrother, R. W., Taylor, G. *Lancet*, Aug. 20, 1960, p. 400.
15. Lawy, H. S. *Ann. rheum. Dis.* 1960, **19**, 42.
16. Todd, E. W. *Brit. J. exp. Path.* 1932, **13**, 248; *J. Path. Bact.* 1938, **47**, 423.
17. Coburn, A. F. The Factor of Infection in the Rheumatic State. Baltimore, 1931.
18. Stollerman, G. H., Lewis, A. J., Schultz, I., Taranta, A. *Amer. J. Med.* 1956, **20**, 163.
19. Anderson, H. C., Kunkel, H. G., McCarty, M. *J. clin. Invest.* 1948, **27**, 425.
20. Stetson, C. A. Streptococcal Infections (edited by M. McCarty); p. 208. New York, 1954.
21. Rantz, L. A., Maroney, M., di Caprio, J. M. *Arch. intern. Med.* 1951, **87**, 360.
22. Holborow, E. J., Isdale, I. C. *Lancet*, 1956, i, 649.

BROILERS

So long as the sale of animal feeding-stuffs was controlled, "chicken farmer" meant in the main an egg producer who sold his time-expired hens as boiling-fowls. Since then the housewife has had to be persuaded that the young and tender fowl is no longer a luxury, and the "broiler" trade has been launched successfully.

The idea, the methods, and the sales talk came from the U.S.A., and if they have had no other effect they have reduced the price of chicken meat by about a third. Success depends on selective breeding, scientific feeding, and low labour costs. The unsexed chicks are run in batches of 15,000 or so and put on the market when 10 weeks old. They are housed in buildings designed for the purpose with controlled (often automatic) heating and ventilation. The manual operations in feeding and watering are reduced as far as is possible. Such "chicken factories" are as vulnerable to the spread of infectious disease as boarding-schools or recruit barracks, and no-one knows this better than the operators. Blood-testing of the parents keeps bacillary white diarrhœa (i.e., infection with *Salmonella pullorum*) to a very low level. Coccidiosis is always present but may be held in check by the routine use of sulphonamide drugs. Newcastle disease is an ever-present threat but is said to cause less damage in broiler flocks than in birds on free range. Other ailments—especially respiratory infections caused by viruses—do not kill but do retard growth, and this, in an industry which must work to fine margins, may easily convert profit to loss.

Objections to this trade have come from several sources. Some local authorities have succeeded in collecting rates from the owners on the ground that the process is an industry and not farming. The kind-hearted have talked of cruelty because it is not the method of chicken rearing used by grandmother. Others have spoken of the dangers of "synthetic diets", while the broiler-keepers wish with equal sincerity that they could in fact synthesise the food rather than buy expensive imported stuffs. And now the hygienists point to the dangers to human health inherent in the process.[1]

The chief danger seems to be salmonella infections. These—even excluding those due to *Salm. pullorum* and *Salm. gallinarum*, which seldom cause disease in man—are common in poultry. Most of the infections seem to be endemic, but there is always some risk of new infections derived from feeding-stuffs containing proteinous additives. Man is sometimes infected by eating undercooked eggs, but infections due to eating chicken meat seem almost unknown in Great Britain. In the U.S.A., however, such infections are reported from time to time (there the annual per-caput consumption of poultry meat is 36 lb. compared with 9 lb. here). Some operations in the processing of broilers seem likely to spread any infection which may be present, but the risk is unlikely to be great. Even in a state of early decay the musculature of the fowl is singularly free from bacteria. The liver (sold with the broiler) might be more dangerous, and some are so oppressed by the thought that they counsel its destruction: they would do better to cut it fine together with a mushroom and fry it in a roll of fat bacon. The traditional ways of handling the old fowl intended for the table are far more objectionable. It is often killed and processed in filthy buildings by filthy hands with filthy equipment. The health inspector would earn the thanks of all of us if he were to look further into this. It is gratifying to know that some authorities inspect all the poultry meat offered for sale, but it must be difficult to find grounds for condemnation other than incipient putrefaction.

The diseases of poultry transmissible to man are very few. A more serious danger arises from the disposal of the unusable remains: they may not be infectious but they decay quickly, breed flies, and smell horrible. A good deal of this offal can be turned into feeding-stuffs, but the disposal of blood is more difficult.

Those who are anxious about salmonella infections in the broiler house may be comforted by the thought that these are likely to hurt the producer far more than his customers: an industry in which so much money is being invested will run no risks of avoidable infectious disease. Big business has moved in and the small man is going to the wall—like the unthrifty chick. This may be regrettable, but, as in the milk trade, the public health is likely to benefit.

1. Pendry, A. R. *R. Soc. Hlth J.* 1960, **80**, 132. Lee, W. R. *ibid.* p. 135. de Gruchy, P. H. *ibid.* p. 139. Walker, J. H. C. *ibid.* p. 142. Barnes, E. M. *ibid.* p. 145. Wadhams, E. H. C. *ibid.* p. 149.

URINARY INFECTION IN UROLOGY AND GYNÆCOLOGY

THE risk of urinary infection after urological and gynæcological procedures involving catheterisation is often regarded as largely inevitable; such infections, it has been thought, stem from a pre-existing inflammatory process in the lower urinary tract; and, with free drainage, permanent damage is unlikely. An investigation by Gillespie et al.[1] however, indicates that many post-operative infections are actually induced by catheterisation and that such infections commonly result in serious complications.

Bacteriological studies of the urine after urological and gynæcological procedures showed that, whereas the organisms sometimes came from the same patient, they more often came from other patients by cross-infection. The principal route of entry was considered to be the urethra or the indwelling catheter lying in it. Precautions introduced to reduce the risk comprised the instillation of antiseptics into the urethra before instrumentation, revision of the methods of disinfecting catheters and cystoscopes, and the introduction of a closed system of drainage in all cases where a catheter was left indwelling.[2] The application of these measures individually in two separate urological units met with different degrees of success, but in combination they brought about a dramatic decline in postoperative infection and morbidity. The rate of infection after prostatectomy was reduced from 83% to 6% and after emergency bladder drainage for acute retention from 73% to 10%. A smaller improvement followed the introduction of closed-bladder drainage after gynæcological operations.

These findings suggest that there is room for improvement in the conventional practice of catheterisation and management after urological and gynæcological procedures, and probably also in the technique of simple catheterisation; and, as Gillespie et al. have shown, such improvement can be effected by fairly simple methods.

Dr. C. F. WHITE has been elected master of the Society of Apothecaries of London.

1. Gillespie, W. A., Linton, K. B., Miller, A., Slade, W. *J. clin. Path.* 1960, **13**, 187.
2. Miller, A., Linton, K. B., Gillespie, W. A., Slade, W., Mitchell J. P. *Lancet*, 1960, i, 310.

Special Articles

ANÆSTHESIA FOR MASS CASUALTIES

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IN providing anæsthesia for the immediate treatment of mass casualties, the requirements are much the same as in everyday work with outpatients. The need is for a few minutes' quiet anæsthesia, with rapid induction and recovery, by a method that can safely be used by anæsthetists of very limited experience. In addition the apparatus should be simple, robust, and compact—so that it can be carried in a haversack, with enough anæsthetic for a score of cases (Stephens 1959).

For nearly a hundred years nitrous-oxide anæsthesia has been used for outpatient work; but in fact nitrous oxide is too weak for this purpose. Moreover, the apparatus needed would be too bulky for war casualties. Of known anæsthetics, the most suitable for either civilian or military use is cyclopropane. The reasons for this choice, with an account of the trial of cyclopropane in 3000 outpatients, are given elsewhere (Bourne 1960).

The main objection to cyclopropane is the explosion hazard; but by mixing the anæsthetic with oxygen and nitrogen in certain proportions this danger is eliminated. The figure shows the apparatus designed by British Oxygen Gases Ltd. for administering such mixtures. For convenience we refer to it as the C.O.N. (cyclopropane, oxygen, nitrogen) apparatus. (In 1955, apparatus that would be more handy to use was devised by one of us in conjunction with Messrs. Sparklets, Ltd. [Bourne 1958]. For civilian purposes at least, it might be preferred to the C.O.N. apparatus; but owing to its higher cost its development has not yet been started.)

The Apparatus

The C.O.N. apparatus * comprises a face-mask, a 6-litre bag, and a simple device for charging the bag with a preset mixture of cyclopropane, oxygen, and nitrogen. Between the mask and bag an angle-piece with a two-way tap allows the patient's respirations to be directed either to the atmosphere or to the bag. A small soda-lime canister for absorbing carbon dioxide is included for administrations lasting longer than about 2 minutes.

The gas mixture.—The gases are contained in a pair of 'Sparklet' bulbs similar to those used domestically for making soda-water. The bulbs are fixed together base to base—one containing the cyclopropane and some of the nitrogen, the other containing the oxygen and the rest of the nitrogen. When discharged into the bag they give a gas-volume of about 5·5 litres, with the following composition:

Cyclopropane	40%
Oxygen	30%
Nitrogen	30%

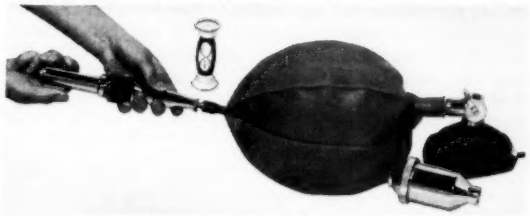
This mixture is non-ignitable; but if it were discharged from the bag into a flame the cyclopropane would catch fire and burn, because dilution with air would bring it within ignitable range. In no circumstances, however, could there be an explosion unless oxygen or nitrous oxide was added from another source. This should therefore be avoided unless oxygen has to be used in an emergency, when the small risk of explosion has to be accepted. (Bulbs containing oxygen only are supplied for emergency use.)

The charging device is essentially a tube, from which bulbs are discharged into the bag, with a piercing needle at each end. One end is closed, and the other has an orifice through which the gases pass into the bag. At this end a simple push-on coupling device with a quick release mechanism, allows the tube to be attached to a non-return valve in the base of the bag during the few seconds needed for discharging the bulbs. The tube is divided in the middle into two parts—the cap and the body—which are coupled together by a screw thread. To charge the bag the paired bulbs are placed in the body, and the cap is then screwed on. As the cap is screwed home the bulbs are discharged in turn—first the cyclopropane, which is only lightly sealed, then the oxygen—regardless of which way they are placed in the tube. (This eliminates the possibility of explosive mixtures developing in the bag during the charging process.)

Method of Use

With the bag empty and shut off from the mask by the two-way tap, the charging device is attached, and the bulbs are discharged. The charging device is then detached and reloaded in readiness for a second administration, should this be needed (see below).

The mask is now applied to the patient's face, care being taken to ensure a gas-tight fit. At the end of a normal exhalation (or, in a large adult, at the end of a forced exhalation) the tap is turned and administration begun.



Apparatus for administering a preset mixture of cyclopropane, oxygen, and nitrogen.

Progress of Anæsthesia

When a patient breathes in and out of a 6-litre bag containing 40% cyclopropane, only the first breath contains this concentration of gas. Later breaths become progressively diluted to a certain level with air from the lungs. The smaller the lungs the less the dilution; hence, with this method, the speed of induction and depth of anæsthesia will be greatest in small children. Both adults and children lose consciousness after three to six breaths; but, whereas in children full surgical anæsthesia is established in about a minute, in adults it may take $1^1/_2$ minutes.

Loss of consciousness is often accompanied by purposeless movements and breath-holding. When the movements subside and regular breathing returns, the patient is in surgical anæsthesia; but the operation can sometimes be started earlier than this.

Provided that no morphine or other central-nervous-system depressant has been given, there is no risk, even in small children, of anæsthesia becoming too deep should administration be prolonged. But if such drugs have been used, there may develop some degree of respiratory depression, which is easily corrected by allowing the patient a few breaths of air. The length of the administration is limited solely by the oxygen supply.

* The apparatus and bulbs will shortly be obtainable from British Oxygen Gases, Ltd., Great West Road, Brentford, Middlesex.

Duration of Administration

With the help of the research and development department of the British Oxygen Company and of Major J. M. Adam, R.A.M.C., we have determined in both adults and children how long administration can be continued before the oxygen falls to an atmospheric level and begins to run short. Details of these experiments may be obtained from British Oxygen Gases Ltd.; the results only will be given here.

In adults the oxygen in the bag falls to 21% in about $3^1/_2$ minutes, and in children under 10 years of age in about 7 minutes. After these intervals, therefore, administration should be stopped and the patient allowed to breathe air. (A sand-glass, like an egg timer, is useful for measuring these intervals.) After administration is stopped, however, anæsthesia will continue for at least another 2 minutes, during which the surgeon can carry on with the operation. There follows a period in which the patient is incompletely anæsthetised; he begins to respond to the surgical stimulus, though he will remain unconscious for a further minute or more.

Thus with a single administration the surgeon is given about 5 minutes' operating time in adults, and up to 9 or 10 minutes in small children. If more time is needed, the bag is emptied and recharged during the period of air breathing. Movement in response to the surgical stimulus denotes the moment for the anæsthetist to reapply the mask and continue as before. This may be repeated as often as necessary, and in this way operations of any length can be catered for.

Comment

By this method, anæsthesia is reduced to its simplest possible dimensions: the anæsthetist has only to apply the mask, maintain a clear airway, and know now long administration can be continued. He is not concerned with how much anæsthetic to give, because the amount is fixed in advance. The method is effective and has a wide margin of safety.

We wish to thank Lloyd-Luke (Medical Books), Ltd., for permission to use the figure.

REFERENCES

Bourne, J. G. (1958) *Brit. med. J.* ii, 47.
— (1960) Nitrous Oxide in Dentistry: its Danger and Alternatives. London.
Stephens, K. F. (1959) *Proc. R. Soc. Med.* **52**, 241.

REMUNERATION: THE WORKING PARTIES REPORT

THE Government agreed to accept as they stand the recommendations of the Royal Commission on Doctors' and Dentists' Remuneration,[1] provided that the professions did likewise. A little later a representative meeting of the British Medical Association accepted this proposal [2]; and two joint working parties subsequently set up to work out details—one dealing with hospital staff, and the other with general practitioners—have now reported. The first of these two reports will be considered by the Joint Consultants Committee on Sept. 13, and the second by a special conference of local medical committees on Sept. 27. Both reports will be reviewed at a special meeting of the Representative Body of the B.M.A. on Sept. 28. The council of the B.M.A. has recommended that these reports and the Minister's offer to implement the Royal Commission's recommendations as a whole be accepted.

1. Royal Commission on Doctors' and Dentists' Remuneration 1957–60. Cmnd. 939. H.M. Stationery Office, 1960. See *Lancet*, 1960, i, 427.
2. See *Lancet*, 1960, i, 1178.

HOSPITAL MEDICAL STAFF

The joint working party recommends that the main salary scales and rates and distinction awards proposed by the Royal Commission [1] shall operate from Jan. 1, 1960. It recommends that the salary of a consultant and senior hospital medical officer first appointed at an age of less than 34 shall be £2550 and £2000 per annum respectively (as for others) but there shall be no increase until the age of 35.

Regional hospital boards.—The salaries of senior administrative medical officers are to range from £3750–4650 in the largest regions to £2780–3360 in the smallest; and the salaries of deputy senior administrative medical officers from £2460–3100 to £2330–2970.

Special allowances.—An allowance of £250 per annum is to be payable to a doctor who holds an appointment, whole-time or part-time, as medical superintendent of one or more psychiatric hospitals. Senior hospital medical officers in consultant posts are to continue to receive an allowance of £550 per annum. Allowances at rates of up to £100 per annum are to be paid to house-officers, senior house-officers, junior hospital medical officers, and registrars holding approved posts in peripheral hospitals.

Residence charges.—For those required to be resident the charges are to range from £155 per annum for a house-officer in his first post to £385 for a consultant; and for those voluntarily resident from £195 to £430 respectively.

Annual leave.—This is to be related to grades. Consultants, senior hospital medical officers, senior registrars, and medical superintendents engaged in administrative duties are to be allowed 6 weeks per annum; and others 4 weeks.

Retrospective payments.—The report includes a formula for the distribution of £9 million in retrospective payment to doctors and dentists employed in hospitals in the period from March 1, 1957, to Dec. 31, 1959.

GENERAL PRACTITIONERS

Retrospective Payments

The £11 million for distribution among general practitioners should be allocated as follows: principals, at the rate of 5·9% of their total gross payments in the period between March 1, 1957, and Dec. 31, 1959; trainees, at the rate of £50 per annum for that period. These payments should be made on, or as closely as possible to, Oct. 31, 1960.

Distribution of Central Pool

Capitation payments.—The capitation payment should be 19*s.* 6*d.* for each person on a doctor's list up to the maximum permitted under the allocation scheme, with a "tolerance" of 50 in respect of each principal. "There should be no immediate reduction in the maximum size of doctors' lists."

Loading payments.—There should be a loading payment of 14*s.* for each patient from the 501st to the 1700th on the list of a doctor in partnership, and from the 401st to the 1600th on the list of a single-handed doctor.

Temporary residents.—The fee for treatment of a temporary resident should be £1 or, where under the Regulations a lower rate is payable in respect of persons temporarily resident in institutions, &c., 10*s.*

Maternity services.—In England and Wales the fee for complete maternity medical services by a doctor on the obstetric list should be 12 guineas, and for such services by a doctor not on the obstetric list 7 guineas.

Rural practitioners' fund.—The rural practitioners' fund (mileage fund) for Great Britain should be £1,880,000 per annum.

Initial practice allowances.—These should be paid for up to four years as follows: first year £1250, second year £900, third year £500; fourth year (subject to the doctor having at least 750 patients on his list at the end of the third year) £250.

Inducement payments.—The net income levels used in assessing these payments should be adjusted so that doctors receiving them obtain increases comparable with those received by general practitioners generally.

Sum reserved for consideration.—A sum of £1 million per annum should be reserved so that further consideration can be given to methods of making the best possible general medical service available to the public. A further working party of representatives of the profession and the health departments should be appointed to consider this matter. (This proposal is welcomed by the General Medical Services Committee in its comment on the report.)

Group practice loans fund.—For 1960–61, £100,000 should be made available to the group practice loans fund from the central pool (this would be additional to the £100,000 credited to the fund by the Exchequer).

Differential payments.—These remain, says the joint working party, for separate discussion. (The General Medical Services Committee remarks that the Royal Commission's recommendation concerning differential payments has proved most contentious, and that, to devise a scheme which might be accepted generally, a great deal more discussion will be required. As this recommendation is open indefinitely the committee commends the proposal to examine it later, and suggests that a special working party be set up.)

The Wider World

GOVERNMENT MEDICAL SERVICES IN SOUTHERN RHODESIA

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THIS account of Government medical services in Southern Rhodesia is the outcome of a visit from March to June of last year. Since then the medical services of the neighbouring territories of Northern Rhodesia and Nyasaland have been integrated, but I must emphasise that I refer only to Southern Rhodesia, and that conditions are in many ways different elsewhere in the Federation.

Southern Rhodesia is situated roughly between latitudes 16 and 25° S and longitudes 25 and 33° E, comprising about 150,000 sq. miles of which 6150 are cultivated. It has a population of $2^1/_2$ million Africans and 200,000 Europeans, together with a few thousand Asiatics. The majority of Europeans live in the two cities of Salisbury and Bulawayo.

Most of the country is over 3000 ft. above sea level; below this height it is termed low veldt, and above, high veldt which is chiefly 4000–6000 ft., with a maximum of 8500 ft. at Mount Inyanga. The high veldt is a particularly healthy district, with hot days and cold nights for the greater part of the year. The low veldt, which is very hot in summer, with many malarial areas, is mostly confined to the three river valleys—the Zambezi, the Sabi, and the Limpopo. The Eastern Highlands are possibly the most delightful region in Central Africa, being not unlike parts of the Scottish Highlands but with a far better climate.

Indigenous diseases include schistosomiasis and amœbic dysentery, found among both Africans and Europeans. Schistosomiasis is a real problem; the only area in which the rivers and streams are not affected is that of the Eastern Highlands, this adding to its attractiveness. Malaria and trachoma are common amongst the Africans, and in one rural area which I visited the doctor said that his first line of treatment for all Africans was antimalarial whatever else was wrong. Trypanosomiasis is common in cattle of the low veldt, and the human variety is seen only among Africans in certain areas. Leprosy is found in low-lying areas, in patches.

MEDICAL PRACTICE

Private practice is found almost exclusively among the European community, although as they improve in economic status a steadily increasing number of Africans are availing themselves of private treatment. The Federal Government medical services cover all the African population and certain European employees of the Government, such as police and all children in Government boarding-schools, but when these children are in hospital a private practitioner is responsible. Another Government service—the railways—has its own service, which is free to employees. Some of the larger mining and industrial concerns have a private scheme for free treatment of their employees. Medical missions are responsible for about 20% of the African population, and these are subsidised from Government funds. All Government services for the Africans are free. Figures will give some idea of the disparity in distribution of doctors among Europeans and Africans. In the city of Bulawayo 110 private practitioners cover about 41,000 Europeans, whereas in the whole of Southern Rhodesia the Government medical service has less than 100 doctors for $2^1/_2$ million Africans.

The Federal Government medical services run along three lines:

Hospitals

In the towns these have all specialist services, especially in the two largest hospitals—Harari in Salisbury and Mpilo in Bulawayo. These are ultramodern institutions, with over 600 beds each. These and other hospitals have opportunities for preregistration appointments, and doctors appointed are flown out and home at the expense of the Federal Government.

Rural Hospitals

These are scattered all over the territory away from the towns. They are generally of 48 beds, with outpatient facilities, and they are under the sole control of a Government medical officer, who is aided by trained African orderlies, nurses, and technicians capable of doing blood-counts and sputum and urine analyses. In a very few cases the work is done on a part-time basis by a local practitioner in a neighbouring town, as at Wankie. The area served by these rural hospitals is often large, and in some cases the medical officer may have to go as far as 90 miles over bush roads to a subsidiary clinic. There is a field for a very wide extension of these services to cover the vast number of Africans requiring treatment.

Public-health Officers

Each is responsible for a very large area.

Candidates for the Government Medical Service, after acceptance, do a term of service in one of the two hospitals, Harari or Mpilo. This lasts for some months during which they do various work in the hospitals or schools and medicolegal work, and at the end they may be sent as a locum to a rural hospital. After a variable period vacancies are advertised and the officer may volunteer or be posted to one of the rural hospitals.

Work in the hospitals is much the same as in England, except for the prevalence of nutritional diseases, including kwashiorkor, among the children, and the ever-present schistosomiasis. The officer is considerably assisted by African-trained orderlies, and some of these impressed me very much by their clinical acumen. They are also invaluable in interpreting the many dialects. In some of the larger centres, corresponding to a large village in this country, the officer may have to supervise a hospital for Europeans, staffed by European nurses.

A typical centre comprises a rural hospital and an unfurnished house for the doctor. The Africans come or are brought to the clinic for inpatient or outpatient treatment. Domiciliary work in the African villages is

impossible owing to the distances and the amount of work. The job is full time, and the doctor is on duty for 24 hours a day, though he can get time off by arranging for a neighbouring colleague to stand in. This rural hospital work is very rewarding, and the amount of work that can be done by an enthusiastic man is amazing. He is his own boss, with much independence. In surgery he has the widest powers, or he can send the more difficult cases to the nearest town hospital.

I visited three of these rural hospitals.

At Shabani, the centre of a large asbestos-mining area, the officer is responsible for a European hospital and has quite a lot of private practice. In other areas where the European population is too small, an allowance of £200 is made.

The second was at Ndanga, a very out-of-the-way place 45 miles from Fort Victoria, where the officer was on the point of retiring after 32 years' service. There Dr. J. H. Kennedy gave me one of the most interesting afternoons of my life, recounting his experiences. If he could be persuaded to put them in a book, I feel sure it would prove a best-seller. He had a subsidiary clinic at Triangle, 90 miles away, over the roughest bush roads, passable only in a jeep.

The third rural hospital I visited was Matobo, in the Matopo hills, and only 25 miles from Bulawayo. The proximity to Mpilo hospital and all its facilities made it different from the others. There are also remote places such as Gokwe, 80 miles from the nearest town, with a tiny European population comprising a native commissioner, British South African Police, and, possibly, a European storekeeper. A community like this has to make its own recreations and social life.

For the doctor considering such a service there are great advantages. The medical work is intensely interesting and varied—more so than in this country. Disease is seen in the stage that doctors saw it here 70 years ago—i.e., much later than in this country. The doctor there has much more independence without the fear of medical service committees. Income tax is considerably lower, and the excellent educational facilities are free. For those in remote areas boarding arrangements can be made at a cost of £25 a term. The standard of living is high, domestic servants are plentiful, cheap, and good. There is much social life, possibly because of the lack of television, and visiting is a great feature in the more closely knit communities.

Apart from Salisbury and Bulawayo the roads are not congested with traffic. Almost every European has a car, and thinks nothing of going long distances on a visit to friends. Large areas still teem with game, and touring possesses certain excitement—never knowing what one may meet. The 300 miles of road from Bulawayo to the Victoria Falls is signposted for 60 miles by the Rhodesia Automobile Association " Beware of Elephants ". The long hot sun-drenched days almost all the year round, and the wonderful cool nights when the atmosphere of the high veldt is so clear that the stars seem more brilliant than in these northern latitudes, add a zest to living.

Central Africa still retains some of its age-old mystery. No-one knows the origin or date of the great temple at Zimbabwe, and many mysterious cave paintings remain from the extinct period of the Bushmen. The Africans still venerate their witch doctors, and often consult them before turning to the European for treatment, frequently showing the scars of wet cupping.

In Southern Rhodesia a real attempt is being made to establish a multiracial society, and the Federal Government has Africans training as doctors in this country, but until the multiracial University of Rhodesia can turn out doctors in sufficient number, they must rely on recruitment from the Western world. The need is enormous, and more officers are urgently required. Here is an important way in which we can assist in the creation of better race relations and show our admiration for this great effort to create a real multiracial state in Central Africa.

For further details as to pay, leave, &c., application can be made to the High Commissioner, Central African Federation, Rhodesia House, 429, Strand, London, W.C.2.

I am deeply indebted to Dr. William Sheffield, Director of Medical Services for the Federation; to Dr. Harrington of the Bulawayo General Hospital; to Dr. Wally Warne and Dr. Peter Cushman of Mpilo Hospital; to my son-in-law, Dr. M. J. Binnie, who has rendered invaluable service; and to many others who have given me much assistance.

Occasional Survey

RADIO-FREQUENCY RADIATION

RADIO-FREQUENCY (R.F.) electromagnetic radiation is seldom thought of as dangerous. Medical diathermy has for many years made use of the heating effect of controlled electromagnetic fields, but the ever-increasing use of radar, powerful short-wave radiotransmitters, and industrial high-frequency dielectric heating has exposed many more people to the likelihood of injury. The introduction, some two years ago, of tropospheric forward-scatter radio stations as part of the NATO defence plans aroused some interest in the risks of R.F. radiation; and further importance has been given to the subject by the proposal to establish a ballistic-missile early-warning radar system (B.M.E.W.S.) in this country.

The possibility that radar could cause any injury was, for obvious reasons, denied during the late war. Little official comment was made on the hazards of the NATO transmitters; now, however, the Post Office has issued a code of safety precautions [1] to be observed with sources of intense R.F. radiation.

The microwave frequencies are usually specified in megacycles (10^6) per second (Mc.p.s.), or kilo-megacycles (10^9) per second (kMc.p.s.), and frequency bands by letters of the alphabet. The S band, for example, which includes the commonly-used radar frequencies, extends from 2·4–4·5 kMc.p.s. Some representative frequencies are: " short-wave " diathermy, 10–100 Mc.p.s. (3000–300 cm. wavelength), tropospheric forward-scatter radio, 860 Mc.p.s. (35 cm.), and most radar, 3 kMc.p.s. (10 cm.). Industrial dielectric heating equipment operates at about 25–70 Mc.p.s. (1200–400 cm.).

Rumours that a radar beam is a sort of " death ray " are current in the United States,[2] and are made the more convincing by some of the curious effects of S-band airborne radar, such as the ignition of dry steel wool, and the firing of photoflash bulbs at distances up to 350 ft.

The effect of a R.F. field on the human body is predominantly thermal, and, in 1957, a technician in the United States died from severe internal burns after exposure to a radar beam.[3] A widely-held belief during the late war was that working with radar apparatus could cause sterility. This is possible, but it is unlikely that any sterility would be more than temporary, because, although spermatogenesis may be inhibited by heat, the testis has good powers of recovery from thermal damage.

Recent work in the Universities of Pennsylvania and of

1. Safety Precautions Relating to Intense Radio-frequency Radiation. H.M. Stationery Office, 1960. Pp. 8. 9d.
2. Morgan, W. E. *A.M.A. Arch. industr. Hlth*, 1960, **21**, 570.
3. Electrical Accidents and Their Causes, 1957; p. 18. London, 1959.

California has shown that the radiation effects are more complex than can be accounted for by thermal changes alone. The body is composed of tissues of widely differing electrical conductance, and possesses capacitance, inductance, and resonance, as well as having a wavelength related to its physical size. While this was recognised by early workers on the effects of diathermy, they did not fully appreciate the results of the production of reflections and standing waves as the energy passes from a tissue of one conductivity to that of another—the "interface effect".

At frequencies below 1·5 Mc.p.s., the body seems to be transparent to R.F. radiation. As the frequency increases, the body absorbs more and more power, until a point is reached at which the absorption begins to diminish. Finally, at about 10 kMc.p.s. (3 cm.), the skin acts as a reflector. Penetration is roughly $^1/_{10}$–$^1/_{100}$ of the wavelength—that is, 1 mm.–1 cm. at the usual radar frequency. At 300 Mc.p.s., penetration lies between 1 cm. and 10 cm.; at these longer wavelengths, some 40% of the energy is transformed into heat in the deep tissues and causes catastrophic internal damage without the thermoreceptors of the skin being unduly stimulated, as they would be at, say, 3 kMc.p.s.

The radar cross-section of the body varies with the frequency and is hard to determine precisely. It is about 0·03–2·3 sq.m. at 400 Mc.p.s., and about 0·5–1·2 sq.m. at 9·4 kMc.p.s.[4–6]

The results of animal experiments are not directly applicable to man, since fur-bearing animals, with their different system of heat regulation, seem to be the more susceptible.

Deichmann et al.[7] found that microwaves at 20 kMc.p.s. (1·25 cm.) produce both local and systemic effects in rats and mice, often leading to death. A 45-minute exposure of a rat, at a level of 20 milliwatts (mW) per sq. cm. caused a slight congestion of the lungs, a subcutaneous scrotal temperature of 35°C, and a rise in temperature of 1°C at the dura of the frontal lobe of the intact skull. A 7-hour exposure at 24 mW p.sq.cm. produced leucopenia and an increase in the number of erythrocytes. Some workers consider that the effects of microwave radiation at about 3 kMc.p.s. are the same as those of infra-red radiation, but this conclusion seems to be invalid, at least at 20–24 kMc.p.s.

The eye is much the most vulnerable part of the body, and injury to it is often permanent. The blood-supply of the eye is poor, and it is probable that under the influence of an intense R.F. field the hæmoglobin loses some of its heat-carrying capacity; in addition, heat transfer to adjacent tissues is low. Interface conditions readily arise in the eye and, because of its relatively small anteroposterior diameter, even very short wavelengths can penetrate deeply enough to damage the lens and the retina. Experiments with rabbits' eyes (which resemble the human eye to some extent, though not so closely as do pigs' eyes) showed that damage occurs after even short exposures to 3 kMc.p.s. radiation.[8] Cogan et al.[9] have shown that 400 Mc.p.s. radiation does not produce cataract in rabbits.

Lubin et al.[10] found that the lethal dose of radiation at 400 Mc.p.s. was about 60 mW p.sq.cm. for 30–40 min. for rabbits, and 100–120 mW p.sq.cm. for about 30 min. for rats. Animals receiving repeated exposures to lower levels than these showed no pathological damage, although the possibility of genetic or developmental changes could not be excluded. Boyson[11] has been able to show that doses of radiation, lethal to a number of rabbits out of a group, can produce a variety of pathological changes in the survivors.

S-band radiation is particularly likely to cause cataract, and it is most unwise to look down the open end of a wave-guide operating within this band, even if the oscillator to which it is connected is of low power.[3] Sight-correcting glasses afford no protection, and actually increase the ocular damage because of reflection and focusing of the R.F. energy.[8]

Resonance in the viscera can cause concentration of the thermal damage. Resonance may also arise in the cranial cavity or within the spinal canal, interfering with the normal electrical impulses in the nervous system and leading to loss of motor function.

Living tissue may be affected by the modification of certain protein molecules, as has been shown in vitro. These effects are mainly confined to the 100–300 Mc.p.s. band, and do not occur above 1 kMc.p.s.

According to Schwan and Li[12] "the level of field strength which is dangerous" for a maximum steady flux is 30 mW p.sq.cm. for frequencies less than 500 Mc.p.s., 10 mW p.sq.cm. for frequencies between 1 kMc.p.s. and 3 kMc.p.s., and 20 mW p.sq.cm. for higher frequencies. Some years ago, Holmquest[13] found experimentally that the absorption of 158 watts in 2 minutes represented the limit of tolerance for the human body. If reasonable assumptions are made about the area of the body, this works out at rather more than 15 mW p.sq.cm.

In 1958, the Ministry of Defence suggested that 40 yards in depth would ensure safety in the neighbourhood of forward-scatter radio transmitters, and at the same time NATO proposed a safety level of 0·5 mW p.sq.cm. Shinn[14] considers this distance to be inadequate, and has calculated radiation intensities from transmitters of various types and powers.

He points out that the positions of critical field strength will vary with the type of aerial array. For example, a transmitter radiating 20 kW at a frequency of 860 Mc.p.s. from a 10-metre diameter aerial will transmit a cylindrical beam with an intensity of 46 mW p.sq.cm. and of the same diameter as the aerial for what is known as the "Rayleigh distance"—in this case, 141 metres (just over 150 yards). Beyond the Rayleigh distance, the intensity of the beam diminishes. In forward-scatter transmission, the beam is only slightly tilted up and ground reflection may increase the local intensity of the beam four times. This 20 kW transmitter would project a beam of greater intensity than the Schwan and Li safety factor for a distance of 620 metres (about 680 yards) over level ground up to a height of 6 feet. A 40 kW transmitter would produce a beam with an intensity of 10 mW sq.cm. for about 850 metres (930 yards).

Shinn recommends that forward-scatter aerials should either be at least 14 metres (46 feet) above the ground, or else the beam should be tilted upwards by about $^1/_2°$, that is, by about 0·2 of the beam width.

Bovill[8] quotes a formula which may be used for calculating the danger area of present-day radar systems:

$$R = [(P_w \times G_a) / (4\pi \times L)]^{\frac{1}{2}}$$

where R is the range in centimetres; P_w the average power in

4. Schultz, F. V., Burgener, R. C., King, S. *Proc. Inst. Radio Engnrs*, Feb. 1958, p. 476.
5. *Electronics*, 1959, **32**, 49.
6. *ibid.* p. 38.
7. Deichmann, W. B., Stephens, F. H., Keplinger, M., Lampe, K. F., *J. occup. Med.* 1959, **1**, 369.
8. Bovill, C. B. *Brit. Commun. Electron.* 1960, **7**, 363.
9. Cogan, D. G., Fricker, S. J., Lubin, M., Donaldson, D. D., Hardy, H. *A.M.A. Arch. industr. Hlth*, 1958, **18**, 299.
10. Lubin, M., Cogan, D. G., Curtis, G. W., Dudley, H. R., Bird, L. E., Daley, P. F., Fricker, S. J. *ibid.* 1960, **21**, 555.
11. Boyson, J. E. *ibid.* 1953, **7**, 516.
12. Schwan, H. P., Li, K. *Proc. Inst. Radio Engnrs*, 1956, p. 1572.
13. Holmquest, H. J. *in* Medical Physics (edited by O. Glasser); vol. I, p. 1074. Chicago, 1944.
14. Shinn, D. H. *Nature, Lond.* 1958, **182**, 1792 (quoted by *Times*, Dec. 27, 1958).

watts; G_a the aerial gain-factor (an average figure for this would be about 10,000 or 40 db.), and L is the permissible radiation level (here taken to be 20 mW p.sq.cm.). Thus, a well-known 10-centimetre radar would produce a danger area up to 45 metres (about 150 feet) from the aerial. Actually the transmitter would not be lethal at this range, because the aerial would be rotating at 3–12 revolutions a minute and some cooling of the body, and particularly of the eyes, would take place. The same calculation applied to B.M.E.W.S. gives a range of 3·2 kilometres or nearly 2 miles. Again, the radar might not be lethal at this distance, but the frequency is relatively low, the aerial scans over only 30°, and side-lobe radiation is high. There could, therefore, be deep penetration without thermal warning effects. Taking everything into consideration, B.M.E.W.S. presents a greater hazard to health than any previous radar system.

Cottingham [15] thinks that 10 mW p.sq.cm., based on steady-heat effects and critical temperature, may be too high a figure for complete safety. Schwan and Li allow a 1°C rise of temperature for all tissues and organs, except the eye, where they allow a rise of 10°C. This temperature rise was produced by an intensity of 20 mW p.sq.cm.

The "average" power used in their calculations is probably reasonable for all parts of the body, except the lens of the eye. Assuming that radar pulses last for $^1/_{1000}$ of any period of time, then 10 mW p.sq.cm. represents 10 W p.sq.cm. during each pulse. The pulse duration may lie between 0·1 and 20 μsec., and under these conditions the time taken for the temperature of the lens to rise by 10°C may be very short indeed. B.M.E.W.S. stations employ pulsed doppler techniques, and the pulse length may be as long as 200 μsec. at an average power of 1 megawatt—an even more potentially hazardous state of affairs.

Industrial heating equipment may momentarily subject less vulnerable parts of the body—such as the hands and feet—to absorption greater than 10 mW p.sq.cm. However, the complexity of the field-distribution round these machines is so great that it has not been possible to lay down any permissible limits,[1] and, for the same reason, present radiation-intensity measuring instruments may not be suitable.

The only protection against R.F. radiation that can be afforded to the general public is by the adequate fencing and signposting of danger areas near microwave installations, and by siting the aerials at the top of gently sloping ground or on cliffs overlooking the sea. Protective clothing is available for technicians, and the eyes may be shielded by perforated metal screens. In addition, Morgan [2] recommends that whenever possible dummy loads should be used when transmitters are being tested.

A dosimeter has been developed which absorbs microwave energy in a material simulating avascular tissue, and measures the heat thus produced.[8] A commercially-built radiation monitor is now made for the X band (7·0–11·5 kMc.p.s.), and one is being developed for the 0·3–1·0 kMc.p.s. band.[15] These monitors are sufficiently sensitive to measure R.F. energies in microwatts and can be used by those without any knowledge of microwave radio.

The present official recommendation [1] is that prompt medical examination should be made of any person exposed to an intensity of more than 10 mW p.sq.cm., and special attention paid to the body-temperature and to the state of the eyes. An accurate measurement of the intensity to which the victim was exposed is desirable.

15. Cottingham, J. M. *Brit. Commun. Electron.* 1960, **7**, 419.

Public Health

ESTIMATING HOSTEL NEEDS FOR BACKWARD CITIZENS

A Question of Kinship

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THE legislation of the past half-century has led to the confinement of many of the mentally subnormal in large institutions, but the new Mental Health Act encourages a trend towards retaining them in the family and community. Local health authorities have been asked by the Ministry of Health to submit plans for new hostels. It therefore seemed useful to report our estimate of the need for this form of accommodation based on our study of a group of "educationally subnormal" men and women.

METHOD

106 men and women who had been classed as educationally subnormal at school were studied when they were between twenty and twenty-four years of age. They were a random sample comprising a third of those ascertained in this age-group in Lancashire county and Salford city. We studied their careers from interviews with them and with their parents, and from the records of health authorities, education departments, and social agencies. We also compiled social histories and made clinical, psychological, and biochemical examinations of 50 selected subjects.

Each of these young people was assessed according to the following criteria:

Social dependence.—A man who earned enough to keep himself, who had held a job for at least six months, who could manage everyday transport and money matters, and who made social relationships outside his immediate family, was judged independent. For women a stable marriage was accepted as a criterion of independence.

Support from relatives.—Kin were considered to be "available" when alive and within physical reach, but "effective" only when they provided a home for their children throughout the period of dependence. If a social agency had provided a home for a child, support from relatives was judged as either not available or ineffective. Some subnormal children made excessive demands on their relatives who had not been able to cope with them though normal children had been reared successfully.

Types of care.—*Hostels* which provide substitute homes we considered suitable for patients who need social and industrial training or psychiatric support of a kind they might find while living in their own homes. *Hospitals* we considered suitable only for patients who needed special services, such as nursing, medical treatment, or custodial care for acute psychoses or dangerous aggression. *Disciplinary institutions* such as approved schools might deal with some cases referred through the courts.

RESULTS

Level of Social Dependence

No subject earned enough at fifteen years of age to keep himself. A number took several years to settle down to regular work and a few had periods in approved schools and borstals. Nearly all were partially dependent on

families or social agencies for the first few years after leaving school.

By their twenties, however, 88 subjects were independent. Many were courting or married, and mixed socially with workmates and neighbours; they arranged their own holidays and contributed to the family budget but handled their own share of their earnings.

18 remained socially dependent as adults; none were married and none had made their own friends. Some had been found work, but usually of a sheltered nature, and their daily lives were closely supervised by parents or others. From our smaller intensive clinical study of 50 subjects we would judge that these 18 will be permanently dependent, because of their low level of intelligence, personality, and social response, or severe physical handicap.

Thus all 106 subjects needed some form of support until they had attained full adulthood and 18 needed support as adults as well.

Support from Relatives

83 subjects had relatives who looked after them.

2 youths had been committed through the courts to mental-deficiency hospitals after minor offences, and had spent six and four years there, but are now settled with their families. They seemed to be able to live in the community, and on our retrospective assessment they might well have been treated in the same way as other delinquents.

None of these 83 were thought to need hostel care.

21 subjects had lacked support and had each became the responsibility of the children's department before the age of ten years. For 2 of them, relatives were not available; and for 19 they were ineffective.

(*a*) Six families who had failed to provide a home for 4 boys and 2 girls in childhood did so at adolescence or later. 2 mothers, deserted by their husbands, were brought before the court by the National Society for the Prevention of Cruelty to Children, and their children were placed under the care of the local authority. 2 girls, returned when they grew up and helped to re-establish these homes.

An aunt was able to give one youth a home, in return for a small payment, after her own children had grown and left her free to help him.

3 youths, nearing independence as wage-earners, found homes with remarried parents. Before they returned to their families one had spent two years in prison, and another had spent two years in a foster home. A hostel would probably have helped them each for two years.

(*b*) 7 subjects (2 boys and 5 girls) had lived from adolescence in psychiatric institutions (6 in mental-deficiency hospitals and 1 in a mental hospital). Since our study began, 5 have returned to the community without apparent ill results; 1 young man has absconded and is still at large. The remaining young woman is still in a mental-deficiency institution. She had a conversion hysteria for which she probably needs active psychiatric treatment.

The 2 men and 4 women now in the community, who had an average stay of five years each in institutions, might have spent these years in a hostel.

(*c*) 1 youth became a vagrant. He was enuretic and he had great difficulty in finding a tolerant landlady. A hostel might have helped him over at least three years.

(*d*) 4 young women were successfully placed in residential hospital jobs where in effect they lived a hostel life.

(*e*) 3 young men lived independent lives, serving in the Forces, finding their own jobs and lodgings, and marrying young.

By our criteria these last 7 did not need hostels. Altogether, of those lacking kin support, 5 youths and 4 girls did.

2 subjects, both permanently dependent, made excessive demands on their families.

An imbecile girl was subject to tantrums. Her widowed mother could not stay at home from work to supervise her, nor could she afford paid help, and the girl's outbursts seriously upset the other children. Several trials at home failed and she was finally placed in sheltered employment in a convent. The other subject was a spastic and epileptic youth, now living in an institution for epileptics. His mother, though unmarried, had managed to rear her normal second son.

Both these families were fatherless, but because other children were successfully reared at home this was not regarded as the main cause of the failure of support.

Both subjects needed permanent care with a restricted environment.

ACCOMMODATION NEEDED

From these findings we consider that the following places in institutions were needed:

Hostel care.—5 youths and 4 girls needed substitute homes, the men probably for an average of four years and the women for five.

Hospital care.—1 man and 1 woman needed care in specialised institutions for epileptics or mental defectives; 1 woman needed active psychiatric treatment, but we cannot estimate for how long. (The four years since she turned eighteen had all been spent in a mental-deficiency institution.)

Disciplinary institutions.—2 youths spent an average of five years in hospitals after an appearance in court. Approved schools, over a shorter period, might have met their needs.

These findings were applied to Salford City to obtain general estimates which we offer with reserve because our numbers are small. Rates were calculated per 10,000 schoolchildren.

During the period when the follow-up group were ascertained as educationally subnormal, the average annual rate of ascertainment in Salford was 42 per 10,000 schoolboys. We thought that 5 of 68 ascertained boys (i.e., 7%) needed hostel places for an average of four years. Thus for every 10,000 schoolboys places would be needed for 7% of 42, for four years each—i.e., 12 places after the first four years.

In the relevant years, 25 girls were ascertained annually per 10,000 schoolgirls. 4 of 38 ascertained girls in the study (i.e., 10%) needed places, each for five years. This would be equivalent to 12·5 places, after the first five years and thereafter, for every 10,000 schoolgirls. Fewer girls would need places but they would stay longer.

In special institutions, we estimated that 2 permanent places for dependent patients, 1 for girls and 1 for boys, would be needed each year for each 10,000 boys and girls. The need would be cumulative, and in addition to other such places required by the severely subnormal.

DISCUSSION

Hostels can serve those among the mentally disordered who are not able to live independently, whose families cannot give them support, and who yet do not need hospital care.

Like most young people of fifteen or sixteen, the educationally subnormal seldom earn enough to keep themselves and are dependent until full adulthood. But the educationally subnormal may take longer to reach social maturity than their peers; and in this investigation intelligence testing supports other evidence that intellectual maturity in the subnormal from poor social and family backgrounds may be delayed until the middle or late twenties. (Clarke, Clarke, Reiman 1958.)

88 of our subjects were no longer socially dependent

at the time of follow-up and seemed able to manage their affairs without kin support. 18 were assessed as permanently dependent because of intellectual, emotional, or physical handicaps. Those with intellectual handicaps might have been more correctly classed as imbeciles (or severely subnormal). The age-group studied does not reveal the full need of these dependent cases for support. They are likely to lose their parents at later ages, and effective support will then depend on the ages, the personal and family commitments, and attitudes of other relatives. More places will probably be needed for them in later years.

We found that most of the 21 subjects who lacked kin support needed substitute homes during their extended adolescence and period of dependence. Apart from this lack of support they did not differ significantly from the others in childhood or adult I.Q. scores, nor, in the 10 examined, in physique or clinical status. Their employment and delinquency records, however, were significantly worse. (Stein and Susser 1960). 7 of them had been admitted to psychiatric institutions, against 2 from the 83 subjects whose families provided effective homes for them.

We concluded that homelessness, per se, was probably an important cause of the social deviation which led to admission to institutions, whether or not psychological disturbances due to maternal deprivation (Bowlby 1951) or to predisposition also contributed. Retrospectively none of them seemed to have needed special facilities beyond psychiatric advice, social support, and a home during their temporary dependence.

At present, mental-deficiency hospitals not only provide medical and nursing supervision but also serve as substitute homes and disciplinary institutions. For the educationally subnormal, hostels and foster-homes would probably be more appropriate substitute homes wherever behaviour problems are not exaggerated. Offenders might better be dealt with in ways suitable also for other delinquents.

Though there is a clear distinction in function between the various types of care, a patient might benefit from a trial in more than one institution. Different institutions are likely to be useful at different times. Easy movement between mental-deficiency hospitals, hostels, and the community would therefore be important.

The validity of the calculated rates may be questioned because the sample studied is small; it includes a third of those ascertained in a five-year age-group. But we offer the results because some guide may be better than none.

In assessing this estimate, several other factors must be taken into account.

Firstly, ascertainment rates of educational subnormality vary widely. In Salford, for example, rates have more than doubled in the years from 1946 to 1958. This reflects changes in local diagnostic and administrative practice rather than differences in actual prevalence. In certain areas, some of the cases included in our sample of the educationally subnormal might have been classed as normal, and others as feebleminded and thereby mentally defective, rather than as educationally subnormal.

For this reason, in calculating the need for hostel places, we have taken as denominator the whole school population rather than the ascertained population. We think that the number of cases lacking kin, which determines the numerator, is less likely to vary than the rates of ascertainment, since these cases are particularly liable to be ascertained, whether rates are high or low. To confirm this we made an independent check on the current size of the educationally subnormal population lacking kin support. (Our subjects in the follow-up study were ascertained about ten years ago.) For this purpose we used the number of educationally subnormal children in Salford who are in the care of the children's department or who attend a residential school.

Hostel estimates based on these populations (17 places for boys per 10,000 schoolboys, 9 places for girls per 10,000 schoolgirls) were similar to those we made from our study (12 places for boys and 12·5 for girls). The populations are not the same, since from the children's department we had a cross-section of children in care at a single point in time, while in our follow-up study many children moved in and out of care over the period reviewed. On the other hand, not all those in care will need hostels. Despite this, the two estimates are not seriously at variance. We would favour the higher estimate. A hostel designed primarily for young adults who were educationally subnormal at school could also house other young people who are not backward but who lack kin support.

Secondly, the number of subjects lacking kin support will vary in rural and urban districts, with the standard of living in different towns, and with periods of prosperity and depression. Their need for public support is greatest when economic resources are small, and in young populations, as in areas with a high proportion of working-class families.

Finally, the social adjustment of the educationally subnormal varies with the amount of employment available. (Charles 1953, O'Connor and Tizard 1956.) Our study covers a period of almost full employment. Because of all these variables, our rates may not be applicable in other areas, though the principles on which they are based should hold.

SUMMARY

An attempt to estimate hostel needs has been made from a follow-up study of educationally subnormal young men and women who were assessed on their level of social dependence, the effectiveness of kin support, and the most suitable type of care.

Most subjects seem to have the capacity to lead independent lives and the greatest need was a temporary one for those who had no available and effective kin.

Tentative rates of the need for hostel places were calculated on school populations. Reservations which would affect the use of the estimates are the size of the sample, variations in employment levels, and the comparability of populations.

We thank Prof. C. Fraser Brockington and our colleagues in his department for useful criticism, and Dr. William Watson of the department of social anthropology, Manchester University, who suggested the kin categories. The follow-up study was inaugurated by Professor Brockington and was sponsored by the National Association for Mental Health with a grant from the Halley Stewart Trust to one of us (Z. A. S.). The medical officers of health of Lancashire (Dr. S. C. Gawne) and of Salford (Dr. J. L. Burn) made the survey possible by seconding field workers (Mrs. Godsell, Miss Edwards, Miss Melsher, Miss Normanton, Miss Perryer, and Miss Sherman).

REFERENCES

Bowlby, J. (1951) Maternal Care and Mental Health. World Health Organisation.
Charles, D. C. (1953) *Genet. Psychol. Monogr.* **47**, 3.
Clarke, A. D. B., Clarke, A. M., Reiman, S. (1958) *Brit. J. Psychol.* **49**, 144.
O'Connor, N., Tizard, J. (1956) Social Problem of Mental Deficiency. London.
Stein, Z., Susser, M. (1960) *Brit. J. prev. soc. Med.* **14**, 83.

In England Now

A Running Commentary by Peripatetic Correspondents

WE spent the whole of Saturday evening in the cellar of the Nurses' Home. Our Local Medical Committee always meet there. We put up with sulphur fumes from the boiler, the sickly pink of the walls, a wobbly ping-pong committee table, and sciatic twinges from the stacking chairs. Amid good company, tobacco smoke, and a pot of hospital tea we get the moans off a principal's chest, the latest medical story, the leg-pulls, and the mutual morale boost to stick it out a bit longer. We feel so honoured that general practitioners should be allowed to cross the actual threshold of Regional Hospital Board premises: perhaps it is some measure of our age that we are trusted in the Nurses' Home rather than the wards.

Anyway last Saturday we went into a huddle with our local pharmacists to discuss the cost of prescribing: Hinchliffe and all that. The chemists looked startled to meet us in such bizarre surroundings—even more startled than at the idea of a get-together—so we all wallowed in old-world courtesy through the first half of the agenda. Then some economy fiend wanted to know what was done with the drugs which a patient did not use. We shifted uneasily in our seats. Of course we overprescribe. Manufacturers' packs may be oddly assorted. Side-effects, or complications, or no response often alters treatment before the first box is finished. Some patients just will not take their quota: others cannot take it with them. But what happens to the unabsorbed balance of the odd £80 million?

George thought it ought to be someone's duty to collect the leftovers and slip them back into stock. The pharmacists retorted not in their shops, thank you. They were not risking their heads rolling with a test prescription on any old blue pills circulating for the second time or more. The ledger accounts, the poison registers, and the D.D.A. were quite enough to handle without dreaming up any haywire scheme for the patient or his executors to flog the sweepings from the bedside table. Even the dispensing doctors looked convinced.

Michael set us off on a new tack by repeating that unused drugs should not be allowed to linger in the patient's home. It encouraged too many competitors in the do-it-yourself game. Too handy for the folks next door with the same sort of abdominal pain or a cold in the head: too risky for the dog with distemper. We were doing fine with the agenda: no happy returns, no stuffing the neighbours, but all rather negative. Discussion wandered on through wild tales of explosions when pills were popped in boilers, hordes of children and cats poisoned on refuse-tips: almost as bad as Britain's atomic waste. We would have been in the cellar all night if someone had not asked the chairman what he did with his own leftovers and all the postal samples. He shrugged his shoulders. "Oh, we keep them in the kitchen drawer in case we get a cold or the dog looks ill." Over to Hinchliffe again.

* * *

Last year I was poor but comfortable, and hopeful of upgrading. The garden demanded one and a half days' unpaid work at weekends. No, it would not help to have a machine: the beds were too small, and any real gardener will tell you that machines might be all right for farmers, but "they ruin the tilth". So I resisted the temptation to play cricket. I put duty before pleasure and my first lumbar disc slipped.

This spring, with a bar to my S.H.M.O., I fell for a handsome red machine. Play cricket? Of course, it's a duty, good for hospital morale. A spot of gardening? Why, certainly, finish the job on Saturday evening—a pleasure! By midsummer, gardening was taking two whole days, for capital equipment must not lie idle. The machine made me tame the jungle, do the grass, the hedge, the firewood and a good turn for the neighbours. I am also a mechanic—and my second disc has slipped.

This Autumn, no gardening, no cricket. For sale—one new cricket bat, one machine with accessories, dirt cheap. My sons can take me train-spotting in a wheel chair.

* * *

One of the most impressive things about life in these United States is the degree of specialisation. Having succumbed to the title of assistant professor and a tempting salary, I arrived here a month or so ago to take over a sizeable subdepartment and staff.

The reagent bottles were covered in grime, so I decided that one of our first jobs would be a gigantic spring-clean. In my exuberance I explained the idea to a technician, who was aghast and pointed out that in the U.S. this was no job for a trained technician. It seemed reasonable to suggest that the diener (glassware washer) should extend his activities to cleaning the outside of reagent bottles and tidying shelves and cupboards, but I soon learned that dieners are not cleaners. The pensioner who moves dirt about from one part of the floor to the other seemed to be the last hope, but he was able to prove that cleaners, being floor cleaners, are not permitted to move or replace bottles on shelves. Yes, you guessed it! The assistant professor spent his first three weekends cleaning all the bottles in his laboratories.

* * *

Conferences are all right if you take them in the right spirit; but, whatever drives people to them, it is certainly not the urge to confer. Speakers, of course, have a sense of purpose, and organisers seek to cover their year's term of office with lustre. Some go to get away from the kids, and others to make friends and influence people. Others really do go from a vague sense of purpose which may be genuine or secondary to a liberal regional-board policy on study leave. But wining and dining plus the opportunity to meet old pals and hear the latest gossip are the predominant reasons.

The affair I am recovering from was typical enough, and lunch-time hospitality permitted a somnolence lasting through the afternoon's papers, disturbed only by the snores of my neighbours. But the high spot of the affair was the delegate's wife, who, faced with a notice: "Toilets, ♂ and ♀", wandered distractedly upstairs and down before finding them mysteriously on that very floor.

* * *

Thumbing through Garrison's *History of Medicine* I found this comment on Trousseau: "A generous interpreter of the ideas of other men." Garrison may have meant it quite nicely. But one is sometimes tempted to make uncharitable use of the phrase. Or could we say of a paper—Trousseau positive?

* * *

Miss T's artificial leg, despite four thick amputation socks, was far from comfortable. Obviously the thing had to be inspected, if only to show that the imperfection was in the prosthesis and not in the surgical planning of the stump. On stooping to pick the leg from where it stood, knee-flexed in disembodied resignation by the couch, some as yet unknown article flew from the pocket of the white coat straight into the small hole of the socket of the limb and sped into the dark cavern of the foot. A rapid inventory revealed that a fountain-pen was missing, and the diagnosis was confirmed by passing the long-flexed proctoscope light into the solitary opening. Leaving a nurse to deal with Miss T's near-hysterical laughter, sister and consultant departed to devise ways and means of removing a fountain pen from an artificial leg. From our experience certain points are worth noting: inversion, with and without shaking, is useless; digital removal is unavailing; but under proctoscope-bulb illumination direct traction by means of a long gastrectomy clamp has, in our series, proved one hundred per cent. (100%) successful.

* * *

In the Garden

SCIURUS CAROLINENSIS

When I was young we fed the squirrels in Regent's Park
But now they're considered one of the worst things that came out of the Ark.
Though actually they came out of the U.S.A.
Which is why they are bigger and of course not Red but Grey.

Letters to the Editor

COLONIAL MEDICAL SERVICE

SIR,—In your columns (July 16, p. 162) you quote the Secretary of State for the Colonies as saying, in reply to Dr. Barnett Stross: "The large territories in East Africa are increasingly using local doctors qualified at the medical school of Makerere."

The contribution from this source should not be overestimated. East Africa has over 20 million people and is served by some 1800 physicians, many of whom do no clinical work. While the Medical School of Makerere College has, in most departments, space and equipment for the teaching of up to 60 students a year, the finances allotted to the school permit only such a level of staffing as limits the intake of students to 30–35 a year. In view of the length of the medical course it now seems most unlikely that the output of doctors will rise to more than 30 a year until after 1970 at the earliest. The limitations of staffing are accentuated by increasing difficulties of recruitment aggravated by the growing disparity in university salaries between the United Kingdom and East Africa. Since any salary increase can only come out of existing resources the possibilities of staff increases appear remote indeed. At the present rate of progress it will be many years before the East African territories will be able to rely for an adequate output of doctors on the Medical School of Makerere.

Kampala, Uganda. J. N. P. DAVIES.

CENTRAL STERILE SUPPLY

SIR,—I read with great interest your leading article on this subject (Aug. 13).

The Central Sterile Supply at the Cambridge Military Hospital, Aldershot, established in late 1944, became in 1956 a unit for research and development purposes. It is primarily a service, as all these sterile supplies are delivered, used, and collected from operating-theatres, wards, departments, and extramural units.

This research unit is highly flexible, in fact a liquid organisation, and, when occasion has demanded (e.g., an Army operational commitment, the introduction of a new method, and even an improvement suggested by a time-and-motion study), it has been reorganised overnight.

It is autonomous and works a night shift for seven nights a week. In consequence "norms" have been raised—for example, syringes. In the Cambridge Military Hospital each syringe is returned for sterilising in a hot-air oven four times per day. Sterilisation by heat (whether by hot-air oven or autoclave) demands trained and responsible technicians. This could be a weak link in the chain of processes in a central sterile supply service.

Gamma-ray sterilisation offers scope as an efficient alternative to the cumbersome heat-sterilisation method and its use could reduce the number of technicians required. This is being investigated at present. Dressing packs are being sterilised by gamma-radiation for use in military medical units (hospitals and medical centres). The success of this trial may well lead to worldwide extension of such benefits to hospitals and field medical units.

The War Office, London, S.W.1. ALEXANDER DRUMMOND.

SIR,—In your leading article of Aug. 13, you mention the role of disposable products in lessening the work of departments engaged in this type of service. One of the most useful of such products, the cartridge containing an injectable preparation of a drug, for use in an appropriately designed syringe, has been strangely neglected by all but a few of the pharmaceutical firms.

All drugs for injection which can be presented in 2 ml. or less of solution or suspension should be available now in cartridges. The manufacturers should agree on a standard cartridge adapted to permit an aspiration test—in fact, a suitable one is already in use. There are no technical difficulties. The difference in cost between cartridges and ampoules is negligible. The advantages are impressive. A week's survey in Carlisle last May indicated that 70% of syringes used were of 2 ml. capacity or less. The enormous relief which the adoption of cartridges for all small injections would afford to syringe services need not be laboured. The cash value of the change would be equally worth while. A cautious estimate, based on the charges published by a commercial syringe service, suggests that our hospital group would save at least £1000 per annum by taking such a step, if it were possible.

How much longer do we have to wait? And why?

Botcherby, Carlisle. D. HUNTER SMITH.

TOXIC EFFECTS OF FURALTADONE

SIR,—We were very interested to read Mr. Lee's letter (Aug. 13) and we would like to record another case with more extensive neurological findings.

A girl aged 10 years was admitted to another hospital on Feb. 11, 1960, with acute osteomyelitis of her right tibia. A large subperiosteal abscess was incised and *Staphylococcus pyogenes* was isolated. She was treated with chloramphenicol, penicillin, and erythromycin until April 27, when the organism was again isolated, but on this occasion it was insensitive to all antibiotics except furaltadone and novobiocin. She was therefore given furaltadone 185 mg. six-hourly for five weeks until June 6. On June 11 she complained of difficulty in swallowing and had nasal speech. Subsequently she developed nausea, vomiting, and nasal regurgitation of fluids. On June 13 she suddenly became breathless and cyanosed after vomiting and we were requested to admit her to our respiratory unit.

On examination at this hospital the patient was fully conscious and slightly pyrexial, and the most significant physical signs were nystagmoid movements of eyes, ataxia of the upper limbs, bilateral dropped wrists, inability to swallow, loss of abdominal reflexes, symmetrical impairment of sensation to pin-prick in the lower limbs, and collapse of the right middle lobe of the lung. Cerebrospinal fluid was normal, virological investigations all proved negative, and there was no porphorinuria.

Bronchoscopy was carried out and thick mucoid material was aspirated. The patient was treated only with vitamins and tetracycline for her chest condition. Very soon she recovered completely, and she was discharged on July 27.

We concluded that the child had an attack of what can best be described as a toxic polyneuritis, and it appears reasonable to incriminate prolonged furaltadone therapy.

Neasden Hospital, London, N.W.10. K. K. HUSSAIN, HILDA KOILPILLAI.

DOCTORS, ADMINISTRATORS, AND THERAPEUTIC COMMUNITIES

SIR,—Dr. Richard Crocket is to be congratulated on his valuable contribution (Aug. 13) to the study of administrative action in the mental hospital. Such an attempt to analyse the administrative tasks which a psychiatrist working in a hospital must undertake is valuable and timely, as all hospitals will be reviewing their present arrangements during the coming months under the impact of the Mental Health Act, 1959.

I welcome his attempt to examine further and extend the

concept of "administrative therapy" which I introduced some years ago. The category of "supportive administration" is a valuable one, and, as he points out, much supportive administration can be done by laymen; in the general hospital, the secretary integrates the activities of departments, makes statements to the Press, and deals with Ministry officials and other tasks which tend to be performed by the senior psychiatrist in a mental hospital. I feel that Dr. Crocket's attempt to separate off "clinical administration" from "administrative therapy" is rather less valuable, and do not think that the differentiation that he makes between them is valid. When a consultant psychiatrist holds a ward staff meeting and discusses with the ward doctor, the sister, and the nurses the attitudes they are to adopt toward an individual patient, is this "clinical administration" or "administrative therapy"? Dr. Crocket defines administrative therapy as work done "at second hand through assistants whom he directs to carry out certain required clinical duties" which fits this example; yet later Dr. Crocket says that administrative therapy as he has defined it has no part to play in the mental hospital.

I would suggest that his two separate functions of "clinical administration" and "administrative therapy" merge into one another and cannot be separated, and that they are an essential part of the work of the doctor who wishes to practise social psychiatry. Every conscientious psychiatrist in a mental hospital, whether ward doctor, consultant psychiatrist, or medical superintendent, spends much of his time practising this administrative therapy, though often he is not aware that he is doing it.

I fully agree with Dr. Crocket that the manipulative administrator anchored to his office chair has little part to play in an active therapeutic community. We all know of medical superintendents who use their office to limit clinical freedom and the development of social experiment. But there is still a need in the most democratic therapeutic community for a spokesman. Dr. Crocket rightly stresses that the developments and innovations arise from the patients, their needs, and their interactions with the junior nursing staff, yet the senior doctor of a therapeutic community such as Ingrebourne Centre, or Belmont, has a job to do as the spokesman formulating the unit's policies, defining its goals, and defending it against the attacks which inevitably come on it from outside bodies. This, I believe, is the very best type of administrative therapy, and Dr. Crocket is an outstanding practitioner.

Most valuable is Dr. Crocket's insistence that the importance of any person in the hospital should be related to their closeness to the patient and the help they can give him. This is far too often forgotten in discussions at "higher levels" where policy is sometimes conceived as being a response to directions coming from the Ministry rather than a service arising from the needs of the patient.

If the Group for the Representation of the Views of Clinical Psychiatrists continue to make thoughtful contributions like this to our thinking in the present time of flux and change, they will deserve the gratitude of all interested in the progress of psychiatric treatment within the institution.

Fulbourn Hospital,
Nr. Cambridge. D. H. CLARK.

SURVEY OF BLOOD-TRANSFUSION

SIR,—The meticulous clinical survey of blood-transfusion reported last week by Mr. Graham-Stewart appears at a particularly appropriate moment, for many who are responsible for hospital blood-transfusion facilities are viewing with concern the rise in consumption.

It is difficult to contrast blood-transfusion requirements in different hospitals unless it is possible to quote figures with reference to the type of inpatient population and surgical load of any given centre. Comparison within a single group can, however, give some indication of altered requirements over short periods during which clinical commitments should not vary. In this context perhaps the figures from St. George's may prove to be of interest and serve as a basis for comparison with other hospitals.

In the five years 1955–59, the number of blood-transfusions has increased. To allow for fluctuation in hospital accommodation reference can be made to blood consumption per occupied bed per year, or it can be assessed per 100 inpatients who have been discharged or who have died in each year. Such total figures, however, are not entirely realistic; for they include the chronic sick, and many acute hospital beds never receive patients who are at all likely to require transfusion. Some allowance can be made for such differing populations by excluding beds permanently set aside for infectious fevers, chronic tuberculosis, geriatrics, and convalescence. The total bed occupancy at this hospital has varied between 509 and 592 during these five years, but, excluding the chronic or non-transfusion categories and referring only to beds in which patients are likely to receive a blood-transfusion, a lower and more realistic figure is available. In 1955 this was disproportionately less (278) than in 1959 (411) because, prior to development, a branch hospital had a higher intake of patients with tuberculosis or infectious fevers (see table).

BLOOD BANK, ST. GEORGE'S HOSPITAL, LONDON

—	1955	1957	1959
Transfusions	642	1193	1361
Total cross-matches	1587	3511	4593
Bottles used	1318	2803	3388
Cross-matched but not used	269	708	1205
Total (overall) bed occupancy	506	533	592
Average daily bed occupancy *	278	340	411
Consumption/bed */year	4·74	8·22	8·24
Inpatient * discharges and deaths	5802	7014	9176
Bottles/100 patients	22·7	39·9	37·0

* For purposes of comparison, only those acute or semiacute beds have been counted in which a patient is likely to receive a blood-transfusion; infectious fevers, chronic tuberculosis, geriatric, and convalescent beds are excluded. Pædiatric beds have also not been included.

The doubled demand for transfusion can be explained by the increased proportion of patients attending with acute or semiacute surgical and medical conditions in 1957–59. What is interesting, however, is the much greater requirement in terms of bottles of blood for each 100 inpatients occupying similar beds and presumably suffering from similar diseases.

These figures can be of general interest only if comparison is possible with other hospital groups of a similar nature, and records of this type are rarely published. The actual wastage-rate at St. George's Hospital is a little under 2%, and this compares well with the country as a whole: with the closer liaison between hospitals near to the regional centre, this waste, expressed as the return of time-expired blood, should be at a minimum; and Murray [1] records a similar figure of less than 2% of 10,000 bottles in Kingston.

A very rough approximation can be made for the country as a whole, if the total number of bottles of blood collected in a given year is referred to the number of patients discharged or dead after occupying beds of similar category. This reference, however, does not take account of the unknown incidence of wastage shown by the return to the regional centres of time-expired blood: this is cited as roughly 10–14% but varies considerably from region to region. If this wastage is ignored, then it would seem that approximately 20 bottles are used each year for every 100 inpatients occupying beds of an acute or semiacute type where the likelihood of blood-transfusion exists.

"Rules of thumb" are difficult to justify, but the following have been circularised within this hospital group as points to be borne in mind before prescription is made:

Never:

Prescribe single-pint stored-blood transfusions in adults.

Transfuse for prophylactic reasons if the Hb is above 11·0 g. per 100 ml. (74%).

1. Murray, D. S. *Brit. med. J.* 1957, ii, 1239.

Rarely:

Transfuse beyond 12·5 g. per 100 ml. (85%). Leave the patient to provide the balance unless convalescence is jeopardised.

Always:

Calculate requirements (one bottle will raise the Hb by 1 g. per 100 ml. [7%]).

Reflect that three bottles is a maximal amount, unless the surgery is either heroic or catastrophic.

Use stored or reconstituted plasma for at least part of routine resuscitation.

Give intravenous iron, unless time is of the essence (250 mg. elemental iron equals one bottle of stored blood).

Remember that, whilst compatible blood-transfusions are safe, about 1% of all recipients face sensitisation.

Hæmatology Department,
St. George's Hospital,
London, S.W.1. J. L. STAFFORD.

SULPHÆMOGLOBINÆMIA AND GLUTATHIONE

SIR,—In answer to Dr. Discombe's interesting letter (Aug. 13), I agree that the majority of patients with sulphæmoglobinæmia take some opening medicine and that this is commonly one of the "sulphates"; but, whether one considers purgation or constipation, his hypothesis is still based on the idea that hydrogen sulphide produced in the bowel passes from there via the plasma to the erythrocyte.

I submit that there is considerable difficulty in accepting this hypothesis for the following reasons (mentioned in my article [July 30]):

1. Haggard's [1] work, which showed that plasma rapidly oxidised hydrogen sulphide and that "in vivo the gas [H_2S] can exhibit no cumulative action when inhaled".

2. Harrop and Waterfield's [2] observations that acute massive hydrogen-sulphide poisoning in dogs (the gas, administered rectally, was absorbed from the large bowel and excreted by the lungs) did not produce sulphæmoglobinæmia even though the dogs were receiving aniline derivatives as well.

These findings indicate that it is difficult for hydrogen sulphide to pass readily from the plasma into the erythrocyte and that neither acute nor chronic release of H_2S into the plasma is likely to produce sulphæmoglobinæmia. I believe that it is more likely that the H_2S is formed intracellularly where it rapidly reacts with hæmoglobin to form sulphæmoglobin which thereafter "persists for the duration of the life of the cell containing it".

I submit further that the hypothesis outlined in my article provides an explanation for individual susceptibility to sulphæmoglobin formation and for the reported occurrence of congenital sulphæmoglobinæmia.

Baker Medical Research Institute,
Melbourne, Australia. A. D. MCCUTCHEON.

RISKS OF DEFERRING VALVOTOMY

SIR,—We agree with Dr. Bannister (Aug. 13) that mitral valvotomy should not be deferred in patients with the symptoms and signs he described as indicating moderately tight stenosis. In our experience, however, moderate breathlessness on exertion (grade 2) usually indicates a valve which will not admit the terminal phalanx of the index finger. This may reasonably be described as severe stenosis and certainly requires operation.

It has always been our policy to advise surgical treatment for a valve of this size, and, except in the early days when certain lessons had to be learned by experience, we have found that accuracy in diagnosis as regards severity of stenosis or of associated incompetence can be achieved in more than 97% of cases.

There can be no doubt that many patients with mitral stenosis still undergo operation when the best time for operation is past. It is often clear from the history and examination at their first attendance that severe stenosis has been present for some time. At operation the rigidity of the valve suggests that the obstruction is of long standing.

Some patients have not previously been under observation but others have been watched for evidence of deterioration, a policy which may be almost as dangerous as that of watching a radiographic shadow in the lung for evidence of change before deciding whether or not the patient should be investigated to exclude bronchogenic carcinoma. In the period of watching there may be deterioration from progressive hypertrophy or dilatation of the heart or from the development of congestive failure, or there may be disaster from systemic embolism or pulmonary infarction.

Also it may reasonably be assumed that unrelieved mitral stenosis leads to progressive changes in the pulmonary arterioles and to rigidity of the lungs. In addition progressive valvular sclerosis diminishes the likelihood of an adequate valvotomy. Once it is reasonably certain that stenosis is severe, surgical treatment should not be delayed. The same arguments may be advanced against undue delay in undertaking operation for re-stenosis.

Great care must be taken over the history because some patients minimise their disability or accept considerable discomfort without complaint. Other factors being equal it can be said that the *earliest* evidence of progressive dyspnœa usually indicates tight stenosis.

Where there is doubt cardiac catheterisation should be carried out, and we have found that a brisk rise in the pulmonary capillary venous pressure on exercise is sometimes a reliable guide to severity even if the resting pressure is normal.

ANDREW LOGAN
RICHARD TURNER.
University of Edinburgh.

ARTIFICIAL INSEMINATION

SIR,—Dr. Audrey Roberts (Aug. 20) completely misses the point. The essence of adultery is concupiscence. Between a donor and recipient who have never met and do not know each other there can be no concupiscence and therefore no adultery.

Crediton, Devon. L. N. JACKSON.

THE "DOUBLE MALE": A NEW CHROMOSOME CONSTITUTION IN KLINEFELTER'S SYNDROME

SIR,—We wish to report the results of a chromosome analysis of a chromatin-positive Klinefelter's syndrome with 48 chromosomes and the sex constitution XXYY. This condition was encountered in a boy of 15 years, admitted to Booth Hall Hospital under the care of Dr. Magnus Thompson.

The boy exhibits a typical Klinefelter's syndrome with normal male appearance, pronounced gynæcomastia, exceptionally high gonadotrophin level, and low excretion of 17-ketosteroids. He is chromatin-positive both in buccal smears and in neutrophils. There are no traits of mongolism, although he is mentally retarded.

In the bone-marrow there is no evidence of mosaicism; 87% of the cells carry 48 chromosomes. The 2 largest chromosomes in group III make a good pair, leaving 7 autosomal pairs

1. Haggard, H. W. *J. biol. Chem.* 1921, **49**, 519.
2. Harrop, G. A., Waterfield, R. L. *J. Amer. med. Ass.* 1930, **95**, 647.

in the group. 1 of the extra chromosomes is thus an X chromosome. Following the Denver classification, group VII contains the other extra chromosome, and the measurements from enlarged photographs give 3 pairs in this group, so the most probable is 2 Y chromosomes.

This is the first case where the source of the error can definitely be traced. The 2 Y chromosomes came from the father, and unless the egg also was abnormal, the sperm must have carried an additional X chromosome, having 3 sex chromosomes and 25 chromosomes in all.

After failure of association between the X and Y chromosomes in meiosis, a quarter of the second-division metaphases will have both the X and the Y chromosome. Delayed separation of the Y, but normal division of the X, gives 1 normal female-producing sperm and 1 with XYY. There is good reason for believing that failure of association of the X and Y is a prerequisite for non-disjunction in the majority of cases. After the successful division of a bivalent at first division, failure of splitting at second usually is a sign of such severe abnormality that this chromosome would be lost in any case. Non-disjunction of univalents (i.e., chromosomes that were not paired at first division), however, is very common.

Since the XXYY constitution is viable, we may expect the XYY male to be so.

Details will be reported soon.

Cytogenetics Laboratory,
Christie Hospital and Holt Radium Institute,
Manchester.

S. MULDAL
C. H. OCKEY.

STERILISATION OF THE DIABETIC'S SYRINGE

SIR,—I have studied Dr. Carter's letter of Aug. 13 with interested appreciation, but with some critical thoughts. For instance, it is not true to say that only one textbook gives definite instructions on this matter. Dr. Henry Dolger's *How to Live with Diabetes* (1958) and my *The Diabetic Life* from 1925 onwards have given perfectly definite instructions. I have been consistently against unnecessary and troublesome boiling and advise keeping the syringe in spirit as quite effective and the least possible trouble. It is not dismantled and is kept with the needle attached in a long spirit-proof container, equally suitable for injections at home or travelling.

In his own hands, Dr. Carter's technique is no doubt admirable and boiling four times a year little trouble, but I feel it unnecessary to employ—and many patients would not observe it—the "no-touch" technique on which he insists; nor do I see how the needle, having penetrated the insulin cap and his own skin purified only by a swabbing of cotton-wool soaked in spirit, can remain sterile.

London, W.1. R. D. LAWRENCE.

ACUTE ADRENAL INSUFFICIENCY AFTER STEROID THERAPY

SIR,—Dr. Stevens (July 30) has provided a timely reminder of the risks of iatrogenic adrenal insufficiency. As he suggested in the final paragraph of his discussion, such risks may be justified in some cases if corticosteroid therapy enables the patient to lead an active life after other forms of therapy have failed; but it is essential that all the medical attendants of the patient who is having or has had a prolonged course of corticosteroid drugs should be aware of the possibility of severe shock after infection, and should be prepared to give antibiotics readily and to increase the dose of cortisone (or its analogue) in that event. Unfortunately it is our experience that the dose of the corticosteroid is often reduced or discontinued when infection develops, in the belief that corticosteroids allow infections to spread.

The acute adrenal insufficiency after steroid therapy can be severe and resistant to treatment and, as Dr. Stevens has shown, may be fatal. The following case is similar in some ways to his third case, and demonstrates, in particular, the intensive treatment which is required.

A man developed purulent bronchitis and wheezing in June, 1956, at the age of 42. He was admitted in September, 1956, with a second attack in which he was acutely ill, and in addition to antibiotics and broncholytic agents he was given prednisone, which improved him considerably, and which was continued in a dose of 5 mg. t.d.s. together with oxytetracycline, when he went home. He improved steadily and the dose of prednisone was gradually reduced, and in March, 1957, he was advised, in the hospital clinic, to stop the drug.

In view of some recurrence of his bronchitis and asthma, however, he soon began the treatment again and continued to take 15 mg. of prednisone per day for two years.

He next attended the hospital on April 28, 1959, when he was admitted seriously ill, in a shocked state. For one week he had had a cold, shivering attacks, and progressive breathlessness. He had continued his work as a brickworks manager until the previous day. On admission he was markedly cyanosed and had grunting respirations at a rate of 50 per min. The skin was moist and there was poor circulatory return to the limbs. The percussion note was impaired at the base of the right lung, and rhonchi and rales were heard in all zones of the lungs. The pulse-rate was 90 per min. and the systolic blood-pressure 80 mm. Hg. There were no signs of congestive cardiac failure. The sputum was foul and purulent. The temperature was 101·2°F (38·4°C).

Treatment with penicillin, streptomycin, oxygen, and intravenous aminophylline was begun at 1.30 P.M. 100 mg. of hydrocortisone hemisuccinate intravenously and two doses of 30 mg. of mephentermine hydrochloride intramuscularly failed to raise the blood-pressure, but the peripheral circulation was not seriously impaired at first. However, at 6 P.M. he developed acute circulatory failure and intravenous administration of noradrenaline was started; the blood-pressure did not rise to safe levels (approximately 120/80) for about one hour and it could be maintained only by infusing 40 drops per minute of a solution containing 24 mg. of noradrenaline per pint. 100 mg. of hydrocortisone was added at 6 P.M. and 9 P.M. and six-hourly thereafter.

Next day he required 20 drops per minute of the noradrenaline solution. Serum-electrolytes were (mEq. per litre): Na 130, K 4·8, Cl 89, HCO_3 17·2; blood-urea 85 mg. per 100 ml. The urine volume for the day was approximately 2100 ml. Corticotrophin (A.C.T.H.) gel was begun in a dose of 40 units b.d.

On the third day cortisone 100 mg. six-hourly intramuscularly was substituted for intravenous hydrocortisone and was continued for four days. The noradrenaline was gradually reduced in dose and in the evening it was discontinued, having been given for forty-eight hours. The systolic blood-pressure remained about 85, but the peripheral circulation was satisfactory and the urine output continued to be adequate. By the eighth day the blood-pressure was 120/80, and next day the serum-electrolytes were normal.

The dose of cortisone was reduced gradually from the seventh day and was discontinued on the twentieth day. Corticotrophin gel was continued in a dose of 40 units b.d. until the twentieth day and then in a dose of 10 units b.d. On the twenty-sixth day the urinary output of 17-ketosteroids was 2·4 mg. per twenty-four hours and of total 17-hydroxycorticosteroids 20·0 mg. A chest radiograph (May 11) suggested resolving pneumonia at the right base.

The patient was transferred to the convalescent home after twenty-eight days (on May 25) and corticotrophin was continued in an effort to reinduce activity in his adrenal cortex. When he went home on June 8, 1959, he was well. Corticotrophin was given for a further week.

On July 8, 1959, he developed a cold and began to have wheezing attacks. The sputum was purulent. Tetracycline failed to benefit him and he was readmitted on July 18 in

status asthmaticus; the temperature was normal. The sputum was rendered non-purulent by penicillin and streptomycin, but the severe wheezing was not relieved by the usual broncholytic drugs. Within a day of recommencing corticotrophin gel (40 units b.d.) (July 21) the wheeze had resolved, and the patient went home on July 24.

Whenever the dose of corticotrophin was reduced he developed an incapacitating wheeze and looked grey and ill; but the blood-pressure remained normal. In November, 1959, his urinary output of 17-ketosteroids was 7·4 mg. and of total 17-hydroxycorticosteroids 6·9 mg. in twenty-four hours while he was having corticotrophin gel 20 units b.d.; a second estimation yielded 5·0 and 3·9 mg. respectively.

By January, 1960, it was clear that his asthma was not going to be improved by doses of corticotrophin which were practicable for long-term therapy, and corticosteroid therapy was begun again; and on a dose of 0·5 mg. dexamethasone q.i.d. he has remained active and fairly well.

Such cases of acute adrenal insufficiency after steroid therapy are probably not as uncommon as the literature (or literary silence) suggests. Certainly the less severe examples are not uncommon in our own experience and that of our colleagues.

The patient we report appears to have irreversible impairment of adrenal function, since prolonged and vigorous stimulation with corticotrophin produced only subnormal amounts of 17-hydroxycorticosteroids, amounts which are fairly certainly inadequate in the presence of a stress such as infection. In the present case the steroid was not discontinued when the acute illness supervened, but the necessity of an increase in dosage was not recognised.

Royal Victoria Infirmary, Newcastle upon Tyne.

T. B. BEGG
A. G. OGILVIE.

THE CONTROL OF TETANUS

SIR,—Dr. Spalding and Dr. Crampton Smith (Aug. 13) describe a near-fatal anaphylactic reaction, which occurred during an intravenous injection of tetanus antitoxin—always a procedure requiring special precautions. It is a necessary and valuable safeguard, in addition to subcutaneous test doses, that an intramuscular injection of part of the main dose should precede the intravenous injection by at least half an hour. We presume that this routine had been followed, though it is not specifically mentioned.

Your correspondents stress the potential dangers of tetanus antitoxin, and realise that the risk of anaphylaxis can be eliminated only by active immunisation. A course of tetanus toxoid must therefore be included in schedules of inoculations for children and adults. We also support their suggestion that it is the responsibility of any doctor who gives tetanus antitoxin to ensure that his patient is at least offered active immunisation later; the interval between the antitoxin and the toxoid should be six to eight weeks. In retrospect, it is of course unfortunate that the patient described had not been so immunised by the casualty surgeon who gave the first dose of serum in 1955. The fact that tetanus developed notwithstanding further prophylactic serum in 1960 indicates that the elimination of the antitoxin had been unduly rapid, as a result of serum sensitisation from the previous dose in 1955. There is considerable variation in the duration of the protection after second and subsequent doses of serum. For this reason, as well as the greater possibility of reactions to serum, it should now be considered essential to follow tetanus antitoxin by a course of tetanus toxoid.

The importance of widespread active measures has been emphasised repeatedly at symposia, B.M.A. discussions at clinical (Norwich) and annual (Torquay) meetings, and elsewhere. The literature of tetanus prevention is now considerable and includes descriptions of serum reactions and serum-sensitivity tests (subcutaneous trial doses), and the indications for tetanus antitoxin or toxoid. The need for personal records, which would be readily available in an emergency, is also stressed.

There appears to be no official objection to local authorities including tetanus immunisation in their programmes under the National Health Service. Many have in fact done so.

Beckenham, Kent.

L. J. M. LAURENT
H. J. PARISH.

INTRAHEPATIC BILIARY ATRESIA

SIR,—Dr. Cotton's interesting case (Aug. 6) is the first reported hitherto in which portal bile-ducts were seen to be present in profusion in a histological section of the liver at an early age, but which had disappeared on repeating the biopsy some years later. This makes the case an unusual one, as the absence of intrahepatic bile-ducts has been reported in a newborn infant.[1] But the description in Dr. Cotton's article of the liver histology, even in the early biopsy (fig. 1*a*) is *not* of a normal appearance, and this is surely significant.

Nevertheless, the clinical course of Dr. Cotton's patient has been comparable to the others which have been described. Though a falling serum-cholesterol and the disappearance of xanthomata can herald impending liver failure, in Dr. Cotton's child in whom there was continued clinical improvement this can hardly have been the case. It has always been difficult in these cases to understand how, in spite of apparent absence of intrahepatic bile-ducts, the jaundice lessens over the course of years, stercobilin reappears in the stools, and the gallbladder may actually contain bile. This latter fact almost excludes the suggestion quoted by Dr. Cotton that there may be a direct excretion of bile pigment through the intestinal mucosa, but does lend support to the hypothesis that alternative excretory pathways become established within the liver even though they are not obvious in liver-biopsy material. Should any more of these cases come to necropsy it will be important to examine, *and report on*, a large number of portal tracts, in order to establish whether or not the apparent absence of bile-ducts is universal throughout the liver.

We are, yours &c., neither Hass as in Dr. Cotton's article and references, nor Hobbs as on p. 295, but

The London Hospital, London, E.1.

LEONARD HAAS
RICHARD H. DOBBS.

*** Dr. Cotton referred to our correspondents' "excellent review" and he will, we know, share our regret that the tribute was marred by these errors.—ED. L.

ORNITHOSIS AND RAILWAY GUARDS

SIR,—The two letters in your issue of July 23 might seem at first to contradict my statement (July 16) that there had never been a case of ornithosis in a racing-pigeon fancier who kept his pigeons under the normal methods.

As the exact nature of the source of infection is not made clear, I have been checking the cases to which my attention had been drawn. On the case reported in the

1. Dahl-Iversen, E., Gormsen, H. *Acta chir. scand.* 1944, **89**, 333.

British Medical Journal in 1952 I have only slight information, but on the recent case reported in the *State Veterinary Journal* this year it is abundantly clear that these were not normal racing pigeons and were not kept in the normal way.

In the first place the two partners had a loft full of pigeons that were either dead or dying. Secondly, it was their habit to feed these birds by placing a pea between their lips and allowing it to be taken by the pigeons. Although pigeon fanciers have considerable affection for their pets, I can assure Dr. Grist that this is not the normal method of feeding pigeons. Thirdly, the paper by Mr. Grant gives some details of the method of competition arranged. If the information is correct, then this particular district of Glasgow has a unique method of competition. It is certainly not pigeon racing as commonly understood. I mention this not in any sense of criticism of the valuable work done by Mr. Grant and Dr. Grist, but merely to show that my contention that normal racing pigeons kept under normal conditions of the sport are not a danger to their owners, and very definitely not a health hazard.

With the assistance of many people, I tracked down the *State Veterinary Journal* to the Ministry of Agriculture, Fisheries and Food, and the editor sent me a cutting for which I was extremely grateful. I was asked to " refrain from reproducing, abstracting or quoting, as the circulation of the unpriced *State Veterinary Journal* is confined to the veterinary staff of the Ministry of Agriculture ". Perhaps this will explain to Dr. Grist why I was not aware of the outbreak of ornithosis in Glasgow. More important, it raises the question of whether such articles should be restricted in this way, particularly since in this case it involves public health, or more exactly considerations of public health. I cannot help feeling that such secrecy is unnecessary and not in the public interest.

I have now had an opportunity of seeing the article referred to by Mr. C. M. Miller in the *British Medical Journal* of 1952. Although the evidence is abundantly clear of ornithosis resulting from pigeons, no indication is given whether these were in fact racing pigeons and not other domestic pigeons, and the fact that the pigeons were diseased may be the result of abnormal husbandry. Again, more information would be welcome, as it is of great importance to emphasise the difference between racing pigeons and other domestic pigeons.

W. H. OSMAN
Editor, *The Racing Pigeon*.
London, W.C.1.

HYDROCEPHALUS

SIR,—Your leading article of July 2 mentions the 46% spontaneous arrest rate found by Laurence in a series of 182 patients untreated surgically. That this is an impressively high incidence of spontaneous arrest is not denied, but let us look at the problem from more than one aspect. One may say that " few treated groups have fared significantly better ". On the other hand, if a cerebrospinal-fluid shunting procedure is done early in the disease is it not possible that the patient with arrested hydrocephalus will survive with a relatively more normal brain?

The recently developed ventriculo-venous shunting techniques, made possible by tiny valves in the tube system to prevent reflux of blood, give promise of a high percentage of functioning shunts. Whether one uses the Spitz-Holter valve or the Pudenz-Heyer valve matters little, but with either method there is a reasonable prospect of preserving the pallium of those patients in whom the hydrocephalic process may become arrested at a later date.

An adequate series of hydrocephalic patients treated with one of these shunting procedures would be invaluable for comparison with the results reported by Laurence. This might tell us whether shunting the hydrocephalic will (*a*) alter the incidence of spontaneous arrest and (*b*) appreciably increase the intelligence quotient or " educability-rate ".

Department of Neurosurgery,
University Hospital, Saskatoon. J. G. STRATFORD.

RELIEF OF PAIN IN RESPIRATORY FAILURE

SIR,—We are indebted to Dr. Semple for his interest in our letter and for his detailed comments of July 23.

We must apologise for not making it clear that all the patients involved suffered from oxygen desaturation (mean oxygen saturation 73·1%, standard deviation 19·8). Under these conditions, of course, small changes in the pO_2 lead to measurable changes in the oxygen content, since the steep part of the oxygen dissociation curve of hæmoglobin has been reached. We would agree that in saturated patients the oxygen content is not as accurate an index, but this is not so in desaturated patients because of the well-known sigmoid shape of the curve. Since the hæmoglobin level must be presumed to be constant over the short period of the measurements we did not feel that our results would be made more clear by expressing them in terms of oxygen saturation (in fact the mean oxygen saturation after ' Pethilorfan ' was 71%, standard deviation 19·2; this is of course not significantly different from the mean figure before administration of the drug). The measurement of carbon-dioxide tension would indeed have been preferable to the carbon-dioxide content: unfortunately at the time the work was carried out facilities were not available to us for estimating blood pH.

Dr. Semple makes some interesting comments about " driving " the respiratory centre with carbon dioxide. It is, however, not universally agreed that this method is a valid one in assessing the respiratory depressant reaction of drugs in ill patients.[1] In any case all our patients suffered from chronic anoxia and presumably as a result were relatively insensitive to changes in pCO_2. It is difficult to know if valid comparisons can be made between the results achieved in these patients and those in hypoventilated normal subjects: in the latter group it has been shown that levallorphan antagonised pethidine-induced respiratory depression.[2]

We do not feel that the references quoted by Dr. Semple in regard to the effects of other opiate antagonist mixtures are in complete agreement with the conclusion he draws. For example, Thomas [3] concludes that " while it is clear that there is some antagonistic effect of levallorphan to the respiratory depressant action of levorphan when these drugs are given together this antagonism does not amount to complete protection ". Schwab [4] comes to a similar conclusion.

As Dr. Semple points out, however, these results do not necessarily apply in the case of pethidine which we studied. Hossli and Bergmann [5] and Swerdlow [6] have both shown that following the administration of pethidine there is an increase in respiratory-rate, a decrease in tidal volume, and a decrease in minute volume. In our series the decrease in tidal volume occurred, accompanied by a rise in respiratory-rate and in minute volume although, as we stated in our letter, these changes were not sufficiently large to be of statistical significance. Some confirmation is given, however, by the similar increase which occurred in peak expiratory-flow rate.

We would have preferred to compare directly, using these indices, the action of pethidine and pethilorfan in the same patients, but, as already noted, the patients in question all suffered from gross respiratory disease and this procedure was not felt to be justified.

It seems that the conditions of our trial were favourable

1. Megirian, R., White, C. W. *New Engl. J. Med.* 1957, **257**, 849.
2. Zeedick, J. F., Foldes, F. F., Rendell-Baker, L., Koukal, L. R. *Anesthesiology*, 1957, **18**, 178.
3. Thomas, D. V., Tenney, S. M. *J. Pharmacol.* 1955, **113**, 250.
4. Schwab, M., Becker, H. M., Koppen, E., Podworny, M., Wagner, P. H. *Arzneimittel-Forsch.* 1957, **7**, 283.
5. Hossli, C., Bergmann, G. *Schweiz. med. Wschr.* 1959, **89**, 863.
6. Swerdlow, M. *Anæsthesia*, 1957, **12**, 174.

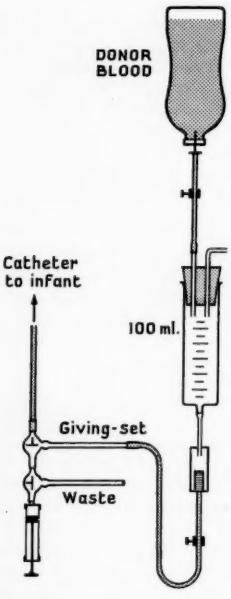
for the demonstration of respiratory depression, should this have occurred; the mechanical indices used were those already shown to be affected by pethidine, and the patients were suffering from oxygen desaturation, any extension of which was likely to produce measurable depression of the respiratory centre, even though this was habituated to high CO_2 levels. The fact that depression was not demonstrated may have been due to the small size of the series examined, but it seems more probable that depression did not in fact occur, in accordance with our previous clinical experience of this mixture. Since it is generally accepted that such depression follows the use of morphine and pethidine alone, our original limited conclusion appears to be justified—" that pethilorfan seems to be a desirable substitute for pethidine or morphine alone in the treatment of patients with severe respiratory disease ".

T. G. JUDGE
J. H. ROLLAND RAMSAY
C. KELMAN ROBERTSON.

Industrial Chest Unit,
Bangour Hospital,
West Lothian.

DRIP METHOD FOR EXCHANGE TRANSFUSION

SIR,—Dr. Norman's letter of March 19 describing a new 2-way automatic glass valve for exchange transfusions prompts us to describe the method we adopted a year ago, and have used in over 180 exchange transfusions.



We let the donor blood run into the infant directly, by including in the drip system a burette for accurate measurement of the blood. The barrel of a 100 ml. all-glass syringe fitted with a two-holed rubber cork is an ideal burette. To the nozzle of this barrel we attach the usual dispensable plastic giving-set with filter. The giving-set is connected to the side-arm of a double 3-way tap while the other side-arm is connected to a graduated cylinder serving as waste bottle.

After the withdrawal of 10 or 20 ml. of blood from the infant a corresponding amount is run in at the desired rate, by gravity, while the syringe is emptied into the waste cylinder and the cycle repeated.

There are many advantages to the method:

(1) Once the set is connected there is no interference with the giving route, so that opportunities to introduce infection are minimised.

(2) The dead space is decreased: it comprises only the catheter.

(3) The blood is introduced at an even rate which can be varied at will. As time is saved by not having to wait to empty the syringe with removed blood and then fill it again with donor blood, a much slower rate of introduction of blood can be used without lengthening the overall time spent on the exchange transfusion.

(4) Mechanical damage to the donor red cells is considerably decreased.

(5) The blood given and removed is measured accurately.

(6) The procedure becomes less tiring for the operator and less skill is required. During the giving phase he is unoccupied and can profitably observe the colour, respirations, and reactions of the infant.

This method has now been used by several operators in our hospital and even the less experienced found it quite easy and had no technical difficulties. Perhaps the greatest compliment paid to the method was the remark of an operator with a wide experience of other methods: " With this method the exchange transfusion has become very unexciting and dull."

We now use polyvinylchloride feeding catheters (Edwards Surgical Supplies Ltd., 83, Mortimer Street, London, W.1) for catheterising the umbilical vein. They have many advantages and we urge those who have not tried them to do so.

TIMOS VALAES.

Alexandra Maternity Hospital,
Athens.

RADCLIFFE TRACHEOSTOMY TUBE

SIR,—In their interesting article last week Mr. Salt and his colleagues have focused attention on irritation caused by chemical or abrasive factors. Though they illustrate two tubes which have given bad and good results respectively, no mention is made of the fact that these tubes have quite different measurements. I would suggest that, however important other factors might be, this difference alone could account for the varying clinical picture.

The important measurement is the distance from the mucous membrane of the anterior wall of the trachea to the skin surface. This distance is unlikely to be less than $^3/_4$ in. in a thin woman, and can exceed $1^1/_2$ in. in a man. With the Radcliffe tube this is a fixed distance and cannot be altered under any circumstances. The photograph of their first tube would suggest that, when it is inserted into any tracheostomy in an adult, the tissues must be compressed. Ulceration of the skin with a moist and infected area around is a likely sequence. The second tube (shown by diagram) has a much longer neck, and, if pressure from the first tube had caused the skin trouble, a quick improvement could be expected on changing over, independent of any difference in the structure of the second tube. We are told that the patient found this more comfortable than any previous tube, though the reason suggested is different from mine.

It would seem however, that, if the tissues are compressed, only harm can follow, and that to be able to vary this measurement is an advantage. The Portsmouth tube [1] offers this advantage and, we consider, several others in addition, one of which is that fresh tubes should be readily available without having to discard unused ones. They are made (by the nursing staff) from Magill tubes as used in the operating-theatres. Photographs giving all details will gladly be forwarded by the physician-superintendent of this hospital if requested.

H. B. C. SANDIFORD.

Priorsdean Hospital,
Portsmouth.

REGIONAL PLAN FOR ACCIDENTS

SIR,—Your annotation (Aug. 20) on the proposed accident service of the South East Metropolitan Regional Hospital Board conveys a misleading impression on the disposal of casualties from major accidents.

You imply that all casualties from a major accident (which by definition in Dr. Fairley's report means an accident involving 50 or more persons) in any part of the region will be treated at one of five comprehensive regional accident centres. In fact the proposal, in the formulation of which I took part, is as follows:

(*a*) Group-I hospitals, the five comprehensive centres containing specialised units for thoracic, plastic, jaw, genitourinary, and neurosurgery as well as general and orthopædic departments, will deal with all cases of major injury occurring within their own particular areas, and in addition with *selected* cases requiring their specialised services resulting from any type of accident elsewhere in the region.

(*b*) Group-II hospitals, of which there will be about 10,

1. Hodges, R. J. H., Morley, R., O'Driscoll, W. B., McDonald, I. *Lancet*, 1956, i, 26.

will likewise deal with all cases of major injury from their own areas, including those from major accidents involving 50 or more persons, but *excepting* those selected cases which require the specialised services that only a group-I hospital can provide.

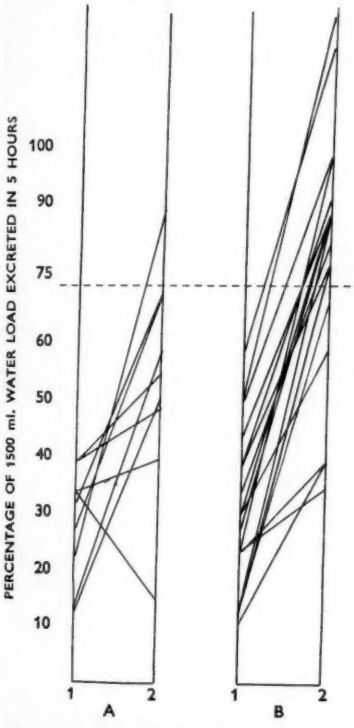
In other words the great majority of casualties from a major accident will be taken to the nearest of about fifteen accident centres distributed throughout the region, and will not have to travel many miles simply to reach a group-I hospital.

Tunbridge Wells, Kent. J. H. MAYER.

FAILURE OF CORTISONE TO CORRECT IMPAIRED WATER DIURESIS IN PATIENTS WITH SUPRASELLAR TUMOURS

SIR,—The impaired water diuresis in patients with hypopituitarism can be reversed by the oral administration of cortisone.[1]

A similar abnormality of water metabolism—that is, a failure to respond to hæmodilution with a diuresis—has been observed in patients with space-occupying lesions in the region of the sella turcica.[2] We have now studied the effect of the oral administration of steroids on the abnormal diuresis in patients of this type.



Percentage of a 1500 ml. water load excreted within 5 hours in nine patients with suprasellar tumours (A) and seventeen patients with hypophyseal adenomas (B), before (1) and after (2) steroid therapy. Group A comprised five subjects with craniopharyngiomas, two with gliomas, and one each with carotid aneurysm and suprasellar meningioma. Three of the patients in group B had acromegaly.

The accompanying figure shows the results obtained in nine consecutive patients with primary suprasellar space-occupying lesions and seventeen patients with pituitary adenomas in whom an abnormally small diuresis followed the ingestion of 1500 ml. of water. In each patient the test was repeated on another occasion after giving 100 mg. of cortisone (or its equivalent) in divided doses, 14 and 2 hours earlier respectively. If less than 80% of the administered water load was excreted in five hours on this regime the test was repeated after a further two or more days of steroid therapy.

Eight of nine patients (90%) with suprasellar tumours failed to restore their diuretic response to normal—that is, greater than 75% excretion within 5 hours—with steroid treatment. By contrast, failure of diuretic response to revert to normal completely was observed in only five of seventeen (30%) patients with pituitary adenomas.

These results suggest that in some cases of suprasellar tumour there is a failure to inhibit antidiuretic-hormone (A.D.H.) secretion in response to hæmodilution. This is in contradistinction to the better known, but rarer, abnormality of water metabolism, diabetes insipidus, which probably results from the destruction by tumour of A.D.H.-secreting cells in the hypothalamus.

1. Soffer, L. J., Gabrilove, J. L. *Metabolism*, 1952, **1**, 504.
2. Crois, H. J. *Brit. med. J.* 1955, ii, 523.

Department of Chemical Pathology, Institute of Neurology, London, W.C.1. VINCENT MARKS.
The National Hospital, Queen Square, London, W.C.1. RICHARD W. HORNABROOK.

SABIN VACCINE AND COMBINED DIPHTHERIA-TETANUS-PERTUSSIS IMMUNISATION

SIR,—Immunisation against poliomyelitis with living attenuated Sabin-type vaccine [1–4] was made compulsory in Hungary at the end of 1959. The Sabin vaccine and combined diphtheria-tetanus-pertussis vaccine are therefore frequently administered simultaneously.

We have studied the response to simultaneous immunisation and the efficacy of the components of the combined diphtheria-tetanus-pertussis vaccine in infants.

Two groups of infants between 3 and 9 months old were selected. Each infant was given intramuscularly two doses, each of 0·5 ml., at intervals of 5 weeks, of the combined aluminium phosphate adsorbed diphtheria-tetanus-pertussis vaccine—i.e., the routine dose used in mass inoculations.[5]

In addition all the infants in one of the two groups were given orally a dose of attenuated living monovalent poliomyelitis vaccine (types 1 and 2).

1. Sabin, A. B. *Advanc. Pediat.* 1958, **10**, 197.
2. Sabin, A. B. *Brit. med. J.* 1959, **1**, 663.
3. Chumakov, M. P., et al. First International Conference on Live Poliovirus Vaccines. Washington, D.C., June, 1959. Pan-American Sanitary Bureau, Scientific Publications no. 44.
4. Chumakov, M. P. *Orv. Hetil.* 1960, **101**, 109.
5. Joó, I., Réthy, L. *Ann. Immunol. Hung.* 1958, **1**, 121.

TABLE I—SIMULTANEOUS ADMINISTRATION OF COMBINED DI-TE-PE VACCINE AND SABIN'S VACCINE: POTENCY OF DIPHTHERIA COMPONENT

Vaccine administered	DI-TE-PE + Sabin	DI-TE-PE (controls)
No. of vaccinated infants	39	46
Categories of immunity:		
<0·01 A.U. per ml.	..	2
0·01– 0·03 A.U. per ml.	..	2
0·03– 0·1 A.U. per ml.	5	4
0·1 – 0·33 A.U. per ml.	10	7
0·33– 1·0 A.U. per ml.	8	10
1·0 – 3·3 A.U. per ml.	11	16
3·3 –10·0 A.U. per ml.	4	5
10·0 –33·3 A.U. per ml.	1	..
Mean value (A.U. per ml.)	1·04	0·79

TABLE II—SIMULTANEOUS ADMINISTRATION OF COMBINED DI-TE-PE VACCINE AND SABIN'S VACCINE: POTENCY OF TETANUS COMPONENT

Vaccine	DI-TE-PE + Sabin	DI-TE-PE (controls)
No. of vaccinated infants	39	46
Categories of immunity:		
<0·05 I.U. per ml.	..	..
0·05– 0·1 I.U. per ml.	..	1
0·1 – 0·33 I.U. per ml.	..	2
0·33– 1·0 I.U. per ml.	..	1
1·0 – 3·3 I.U. per ml.	7	14
3·3 – 10·0 I.U. per ml.	20	16
10·0 – 33·3 I.U. per ml.	10	12
33·3 –100·0 I.U. per ml.	2	..
Mean value (I.U. per ml.)	6·4	4·07

TABLE III—SIMULTANEOUS ADMINISTRATION OF COMBINED DI-TE-PE VACCINE AND SABIN'S VACCINE: POTENCY OF PERTUSSIS COMPONENT

Vaccine	DI-TE-PE + Sabin	DI-TE-PE (controls)
No. of vaccinated infants	39	46
Categories of immunity: Agglutination at 1 in		
<20	..	4
20	3	..
40	5	6
80	6	5
160	5	9
320	6	13
640	7	6
1280	6	2
2560	1	1
5120	..	..
Mean value	466·1	330·4

Serum was taken from each infant before the first inoculation of combined vaccine, and two weeks after the second, and was titrated to determine the immunity conferred by the individual components of the combined vaccine.

In spite of the scarcity of available data we feel justified in concluding that the poliomyelitis vaccine of the Sabin type does not increase the incidence of reactions to the combined diphtheria-tetanus-pertussis vaccine.

Our data show that the simultaneous administration of living attenuated poliomyelitis vaccine and combined diphtheria-tetanus-pertussis vaccine does not impair the immunogenic potency of the latter (see tables I, II, and III).

Also the average levels of immunity obtained are greater than in the controls, and the number of individuals with a lower level of immunity is smaller. This phenomenon seems to show that the living attenuated poliomyelitis vaccine may act synergistically with the components of the combined vaccine.

Humán State Institute for Serobacteriological Production and Research, Budapest.

LAJOS RÉTHY
JÓZSEF MARÓCZI
ISTVÁN JOÓ.

Appointments

BLAKEY, D. H., M.B. Manc., M.R.C.O.G.: part-time consultant obstetrician and gynæcologist, Chesterfield group of hospitals.

COOLING, C. I., M.B. Lond., F.R.C.S.: consultant surgeon, Royal Marsden Hospital, London.

CRAFT, M. J., M.B. Lond., M.R.C.P. Edin., D.P.H.: consultant physician-superintendent based at Oakwood Park Hospital, Conway.

DAVIES, F. J., M.R.C.S. Eng., F.F.A. R.C.S.: consultant anæsthetist, Mid Glamorgan H.M.C.

GIBB, A. G., M.B. Aberd., F.R.S.C.E., D.L.O.: senior E.N.T. surgeon (consultant) based at Dundee Royal Infirmary.

HANLEY, J. A., M.CH. N.U.I., F.R.C.S.: county surgeon, County Hospital, Letterkenny, Co. Donegal.

KIRK, JOHN, M.B. Lond., F.R.C.S.: consultant plastic surgeon, eastern region, Eastern Regional Hospital Board, Scotland.

LAMB, D. W., M.B. Edin., F.R.C.S.E.: consultant orthopædic surgeon, regional orthopædic service based on the Royal Infirmary and Princess Margaret Rose Hospital, Edinburgh.

O'BRIEN, M. J., M.B. N.U.I.: assistant M.O., Liverpool.

SMILEY, W. K., M.B. St. And., F.R.C.S., D.O.M.S.: consultant ophthalmic surgeon, Aylesbury and High Wycombe area department of ophthalmology, Chalfont and Gerrards Cross Hospital.

Colonial Appointments:

BLACK, K. H., M.B., D.P.H.: principal medical and health officer, Hong Kong.

EARL, A. J., M.B. Cantab.: M.O., Uganda.

FILSHIE, I., M.B. Sydney: senior medical and health officer, Hong Kong.

HARNEY, JEAN L., M.R.C.S., M.P.H.: M.O.H., Barbados.

HITCHCOCK, N. J. B., M.B. Cantab.: M.O., Uganda.

HURLY, KATHLEEN, M.B. W'srand: M.O., Hong Kong.

LEE, CHENG ONG, M.B. Hong Kong; principal medical and health officer, Hong Kong.

MCGREGOR, ALAN, M.B. Durh., D.P.H., D.T.M. & H.: deputy chief M.O., Tanganyika.

NEGUS, R. M., M.B. Cantab.: M.O., Uganda.

ROLES, N. C., M.B. Cantab.: M.O., Kenya.

TEOH, THEAN MING, M.B. Hong Kong: principal medical and health officer, Hong Kong.

WYILE, H. W., M.B. Manc., D.P.H.: principal medical and health officer, Hong Kong.

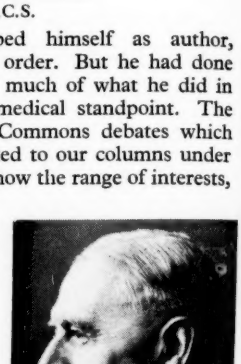
YEOH, GUAN-ENG, M.B. Hong Kong, D.C.H.: senior M.O., Hong Kong.

Obituary

LESLIE HADEN GUEST

BARON HADEN-GUEST, OF SALING
M.C., M.R.C.S.

Lord Haden-Guest described himself as author, journalist, and doctor—in that order. But he had done notable work in medicine, and much of what he did in Parliament was done from a medical standpoint. The weekly accounts of House of Commons debates which from 1939 to 1946 he contributed to our columns under the title of "Medicus, M.P." show the range of interests, the liberal attitude, and the zest which he retained till late in life. Partly because of his independence and partly because his views were wide, rather than narrow or very deep, he never held Ministerial office; but he was a distinguished and valuable back-bencher in the Parliamentary tradition to which he was devoted.



Elliott & Fry

The son of Alexander Haden Guest, L.R.C.P., he was brought up amid the poverty of the Lancashire cotton towns by a father who was a radical reformer. Even as a youth he was lecturing on social problems and in the Labour interest. But when he qualified from the London Hospital in 1900 the South African war was still in progress, and he went out to South Africa as civil surgeon. Enterprising and adventurous, he stayed in Africa after the war, as acting district surgeon and medical officer of health for Ventersted, Cape Colony, and acting railway medical officer at Burghersdorp.

When he came back to London, Haden Guest applied the same enterprise—and also his unfashionable socialist ideas—to improving the care of children. In Southwark he developed what became the pilot model for school clinics. The Fabian Society published his *Case for School Clinics* in 1910, when he was already a school medical officer under the L.C.C., and he wrote much on school inspection, treatment, and feeding. He was medical superintendent of the St. George's Dispensary and School Clinic, Blackfriars.

It was characteristic that by September, 1914, he should already have organised the first Anglo-French hospital (in a Paris hotel), and he was soon founding and directing others at Limoges and Nevers. He also helped to start the Anglo-French Committee of the British Red Cross and Order of St. John, and as its secretary he raised money and organised hospitals for British, French, and Belgian troops and Belgian civilians. Later, in the Royal Army Medical Corps, it was again characteristic of this apparently fearless man that he should win the Military Cross for rescuing wounded under fire at Passchendaele.

After serving in Egypt and Palestine in 1918, he resumed his medical and political work in London, where from 1919 to 1922 he was on the London County Council. As secretary and medical officer to a Labour delegation to Russia in 1920, which included Bertrand Russell, he met many of the Bolshevik leaders; and his long report in our columns [1] emphasised the need for medical help rather than military intervention.

Elected to Parliament in 1924, he became Parliamentary private secretary to the Minister of Health in the first Labour Government, and in the following year went to Canada and Newfoundland as a member of the Empire Parliamentary Delegation. The Empire and Commonwealth were always

1. *Lancet*, 1920, ii, 159, 518, 561, 617, 661.

much in his mind, and it was over the Labour Party's acquiescent attitude towards Shanghai that he resigned from the party, and fought an unsuccessful by-election as an Independent Constitutionalist, in 1927. His next by-election was fought as a Conservative; but by 1931, when he reported on Russia in Reconstruction,[2] he had returned to Labour. In 1933 he was elected member for North Islington, a seat which he held till he was created a peer in 1950.

Founder of the Labour Party Commonwealth Group, he was a member of the West African Commission which visited Nigeria, the Gold Coast, and neighbouring countries in 1938–39. Already before the late war he was much concerned with preparations for air-raids and for evacuation of the civilian population. In 1940–42, while continuing his Parliamentary duties, he again held a commission in the R.A.M.C. and in 1945 he became chairman of the Medical (Personnel) Priority Committee, in which capacity, and as chairman of the National Medical Manpower Committee, he was in close touch with the Services and travelled widely. He was a delegate to the Food and Agricultural Conference in Washington in 1946.

He was created a Lord-in-waiting in 1951 and was vice-chairman of the Medical Parliamentary Group.

In the House of Lords, Haden-Guest was soon as much at home as in the Commons. A man of fine presence and always well-groomed, he had a taste for ceremony which seemed at first a reaction from his republican father. But he could show that traditional usages often have particular value in a time of rapid change, and the conventional appearance was perhaps a little misleading in one who remained so buoyant and even boyish—always ready to go off on a new quest, preferably at the ends of the earth. He had never looked his age, but he was 83 when he died last Saturday.

Dr. Haden Guest married in 1898 a daughter of Max Low. Of their two sons, Stephen Haden Guest, who is in America, succeeds to the title. His second marriage, in 1910, was to a daughter of Colonel A. Goldsmid. Of their three children David Guest was killed in the Spanish civil war, and their daughter, Angela, is a member of the medical profession. In 1944 he married Edith Macqueen, the historian.

HAROLD KINGSTON GRAHAM-HODGSON

K.C.V.O., M.B. Durh., F.R.C.P., F.F.R., D.M.R.E.

Sir Harold Graham-Hodgson died on Aug. 21, at the age of 69, in the Middlesex Hospital, London, where, through his work as director of the X-ray department and latterly as a governor, he has left an imprint of his professional and administrative skill.

The son of the late Dr. G. Graham-Hodgson, of Eastbourne, he was educated at St. Edward's School, Oxford, and Clare College, Cambridge. On the outbreak of war in 1914 he interrupted his medical training to go to France as a despatch-rider; but at the end of that year he was persuaded to return to this country, and two years later he qualified M.B. in the University of Durham. As a battalion medical officer he returned to France, where he remained until wounded in 1917. In the following year he was posted as radiologist to the Second Northern General Hospital at Leeds. After demobilisation he was for a time in general practice in Chislehurst; but from 1922 onwards he devoted himself to radiology. In 1923 he joined the staff of the Central London Throat, Nose and Ear Hospital, and in the following year he became director of the X-ray department of King's College Hospital—appointments which he held until 1934 when he was invited to become director of the corresponding department at the Middlesex Hospital.

At The Middlesex, with the help of a large donation, he had the opportunity of redesigning and reorganising the department. This opportunity he seized; and the department he formed has served as an example for many other hospitals. In diagnostic radiology his interest centred mainly on the nasal sinuses and the early diagnosis of cancer.

2. *ibid.* 1931, ii, 1147, 1203, 1255.

In 1929 he was called in by Lord Dawson to examine King George V during his illness, and was appointed C.V.O. In 1932 he became M.R.C.P., and five years later he was elected to the fellowship. He was a foundation fellow of the Faculty of Radiologists when this was established in 1939, and he held office as president of the section of radiology of the Royal Society of Medicine. In 1952–53 he was chairman of the medical committee of the Middlesex Hospital. After the late war he travelled extensively, lecturing in many countries. He received a knighthood in the Royal Victorian Order in 1950.

A colleague writes:

"Graham-Hodgson's specialised work on disease of the nasal sinuses and bone did not prevent him from keeping abreast of medical progress, and his diagnostic ability was well recognised and appreciated by his colleagues. The loyalty, admiration, and affection of his staff was earned by an unfailing interest in their progress, and by his readiness to help and advise them at all times. The news of his death, five years after retirement, came as a shock to his colleagues, so alive and youthful did he continue to appear to them on his occasional appearances at lunch in the board-room.

"With a background of a Scottish upbringing, he grew up with a love of that country, of its folk, and of fishing. He liked to recall his first salmon which pulled him, 'a nipper of twelve', into the river and downstream until they were both rescued by the station-master. Very different was the scene on a sunny day in August, 1953, on a stretch of the Deveron, which a colleague had thrashed unsuccessfully all day. Towards evening Graham, having spent the day in a neighbouring town, came to the river side and remarked that he had promised a fish for the proprietress of the hotel. Within the hour he had landed a 22-pounder. During recent lecture tours, which included Turkey and Chile, a rod always accompanied him, but it was to the Tweed he turned each spring with the zest of youth.

"Graham-Hodgson possessed attributes which would have taken him far in any sphere of life—enthusiasm, astuteness, a warm personality, and above all an ability to get things done. No better instance of the last can be given than his honorary treasurership of the First International Congress of Radiology, held in London in 1950, when his persuasive powers resulted in an ample surplus. These attributes were allowed play in fields other than medicine—notably in his membership of Lloyds and in his interest in the Stock Exchange, the latter resulting in advice to his friends from which they almost invariably benefited. However, it was in his farm in Berkshire that he derived most pleasure, especially after retirement.

"A man with interests so wide and with such a gift for friendship, he will be deeply missed, not only by his colleagues at The Middlesex but by innumerable friends in this country and abroad."

In his years of retirement he lived in the country; but he rusticated only in a limited sense, as H. S. S. makes clear:

"Graham was good at whatever he did, whether it were medicine, pig-keeping, sailing a boat, fishing, gardening, or any of his many activities. These included, in his retirement, helping me with busy N.H.S. surgeries, and handing out medicines, certificates, and advice without the slightest feeling of the job being beneath his high position in medicine. He brought to everything the same sturdy common sense, backed by a fine brain, which often enabled him to cut the Gordian knot, and which put him in the top rank of the particular art. He had, too, the gift of friendship, of liking and being liked, which means that he will be mourned and missed in many circles and by many people of all occupations. 'And he that is courteous, kind and gentle hath favour in every place.'"

Sir Harold was twice married: first in 1917 to Winifred Elizabeth, daughter of George Jenkins, of Newcastle upon Tyne, and secondly in 1943 to Rosa Dorothy, widow of Frank L. Hallam. There were a son and daughter of the first marriage.

Notes and News

DEVELOPMENTAL LEVELS IN INFANCY

THE importance of being thoroughly conversant with the normal before attempting to diagnose the abnormal has become increasingly recognised in recent years. The early diagnosis of abnormal development has become much more important because of the recognition that certain forms of mental subnormality are now amenable to treatment, and that specific sensory defects, such as partial deafness, should be treated as early as possible. It is generally agreed that cerebral palsy should be treated early, in order to prevent deformities and perhaps abnormal patterns of movement. All these conditions can be diagnosed by simple developmental tests which should be a routine part of every examination of a baby in an infant-welfare clinic, in general practice, or in children's units.

In a useful summary of the developmental stages to be expected in infancy, Dr. Mary Sheridan [1] describes the usual level of development at the age of 1, 3, 6, 9, 12, 15, 18, 24, 30, 36, 48, and 60 months. One virtue of this booklet is that it tells of important skills which can be elicited without any special equipment or accommodation. The booklet will prove very useful to those concerned with handling young children.

University of Cambridge

On July 30 the following degrees were conferred:

M.D.—A. M. Barrett, Judith M. Fitzsimons, D. G. Montefiore, T. J. S. Patterson, *Roger Smith.
M.B., B.Chir.—*John Fletcher, *L. F. Prescott, W. D. Riding.
M.B.—G. H. Evans, Pamela M. Hill, R. H. Morgan.
* By proxy.

Royal Faculty of Physicians and Surgeons of Glasgow

The D.C.H. has been awarded to the following:

Biplab Kumar Basu, Debabrata Bagchi, Keong Aik Ch'ng, Jatindranath Gohain, R. F. B. Lees, K. E. Le Page, S. Wing-Chiu Leung, Muhamed Taque Marashi, Brij Gopal Mehrotra, Pormomilla Lakshnana Murthy Mohanamba, N. A. McC. Somerville, N. V. A. Wickramasinghe.

Society of Apothecaries of London

Dr. C. F. White has been elected master, with Mr. A. M. A. Moore and Mr. T. K. Lyle as wardens.

The following diplomas have been granted:

L.M.S.S.A.—J. G. Shores, T. Tut, D. E. Alder, J. Reuvers, K. C. D. De Silva, J. H. Romano, S. R. Meadow, R. S. Cormack, B. Ibrahim, I. Hosny, R. W. D. Gomes, R. G. Gibson.
D.I.H.—J. W. R. Battram, S. Boydell, M. M. El-Attal, P. R. Gilbert, R. V. Havard, D. J. Llewellyn, S. J. A. Luckas, A. D. McIntyre, T. Myint, J. F. Taylor, J. D. Thomas.

On Wednesday, Oct. 19, at 5.30 P.M., Mr. T. Holmes Sellors will give the Joseph Strickland Goodall lecture at Apothecaries' Hall, Black Friars Lane, E.C.4. His subject will be the evolution of intracardiac surgery.

Faculty of the History of Medicine and Pharmacy.—The Maccabæans are enabling this faculty to offer an annual prize of not more than 25 guineas, with a bronze medal, for the best original essay on a subject connected with the history of medicine or pharmacy written by an undergraduate or graduate under the age of 30. Further particulars may be had from Dr. F. N. L. Poynter, Wellcome Historical Medical Library, 183, Euston Road, N.W.1. Those wishing to compete are asked to send their names to Dr. Poynter before Sept. 15.

British Diabetic Association

Medical and Scientific Section.—This section is to hold a colloquium on prediabetes at the Royal Faculty of Physicians and Surgeons, Glasgow, on Oct. 14. On Oct. 15 original papers will be presented on aspects of diabetes in general. Particulars may be had from the local organising secretary, Dr. M. J. Riddell, Victoria Infirmary, Langside, Glasgow.

Parliamentary Private Secretary

The Minister of Health, Mr. J. Enoch Powell, has appointed Mr. Marcus J. Worsley to be his Parliamentary Private Secretary.

1. The Developmental Progress of Infants and Young Children. By MARY D. SHERIDAN. *Rep. publ. Hlth med. Subj., Lond.* no. 102. H.M. Stationery Office. 1960. Pp. 11. 1s. 3d.

American Thoracic Society

Applications for next year's grants for medical and social research in tuberculosis and other respiratory diseases will be received by the National Tuberculosis Association, through its medical section, the American Thoracic Society (formerly the American Trudeau Society), up to Dec. 15. Information may be had from the division of research and statistics at the society's office, 1790, Broadway, New York 19, N.Y.

The annual meeting will be in Cincinnati on May 22–24. Prospective contributors should write to Dr. Leon H. Schmidt at the same address.

Biology of Space Travel

On Sept. 29 and 30, at the Royal Geographical Society, Kensington Gore, London, S.W.7, the Institute of Biology is holding a symposium on this subject.

The topics to be discussed include the effects of high gravitational forces during the take-off and re-entry of space vehicles; the functioning of the body in extremely low gravitational fields; maintenance of life in space ships; radiation in space and its effects on man; psychological problems of solitude and confinement; the human brain in space time; dangers of contamination of planet and the earth; and the probable environment on other planets and its suitability for some forms of life. The speakers will include Air Commodore W. K. Stewart, Wing-Commander T. C. D. Whiteside, Flight-Lieutenant John Billingham, and Dr. P. H. A. Sneath. Further details may be had from the Institute, 41, Queen's Gate, S.W.7.

Extrapyramidal System and Neuroleptics

A symposium on this subject, organised by the department of psychiatry of the University of Montreal, is to be held at the university on Nov. 17–19. Further particulars may be had from the secretary of the symposium, Dr. Jean-Marc Bordeleau, department of psychiatry, University of Montreal, Quebec, Canada.

Family Life and Family Practice in the U.S.S.R.

On Friday, Sept. 16, at 8.30 P.M., at 1, Wimpole Street, London, W.1, Dr. J. H. Hunt will give a lecture on this subject to members of the College of General Practitioners. Tickets may be had from the secretary of the college, 41, Cadogan Gardens, S.W.3.

The Coventry and District Voluntary Blood Donors' Association is to make an award of £50 or two awards of £25 for an "outstanding contribution to the knowledge of blood transfusion or the science of hæmatology". The award is open to any person, of any age or nationality, for work done in Great Britain. Applications or nominations should be sent to the hon. general secretary of the Association, Mr. L. G. Griesbach, 6, Delhi Avenue, Coventry.

The *Journal of Mental Subnormality* is the new title of the periodical which since 1952 has appeared as the *Journal of the Midland Mental Deficiency Society*. It is published twice yearly. Subscriptions (15*s.* per annum) may be sent to the publication office of the journal, Monyhull Hospital, Kings Heath, Birmingham, 14.

CORRIGENDA: *Bruxism and Chronic Headache.*—The paper by Dr. Berlin and Mr. Dessner in our issue of Aug. 6 describes a "relaxation plate" which makes it impossible for the patient to clench his teeth. The authors point out that their description can be misunderstood. The sentence adjoining their illustration should read: "The bite-plane is of such thickness that, with the mandible in rest position, a freeway space of 0·5–1 mm. is left anteriorly."

Simplified Method for Detecting Formiminoglutamic Acid in Urine as a Test of Folic-acid Deficiency.—In the paper published on Aug. 13, by Dr. Knowles, Dr. Prankerd, and Dr. Westall, the word "amps" should read "milliamps".

A Local-anæsthetic Solution with Longer Action.—In this article by Dr. R. E. Loder (Aug. 13, p. 346) the account of the preparation of the solution should have begun with the words: "0·5 g. lignocaine hydrochloride is stirred into 50 ml. 10% dextraven until dissolved, placed in a 50 ml. bottle . . ."

Births, Marriages, and Deaths

BIRTHS

MUNRO—On Aug. 23 to Olive and Ian Munro, of Sevenoaks, a son.